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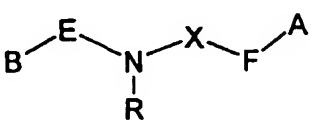
(54) Title: NOVEL AROMATIC AMINES AND AMIDES ACTING ON THE MELANOCORTIN RECEPTORS



(I)

(57) Abstract: The present invention relates to novel aromatic amines and amides of general formula (I) and to the use of these amines and amides for the treatment of obesity, anorexia, inflammation, mental disorders and other diseases associated with the melanocortin receptors or related systems, e.g. the melanocyte stimulating hormones.

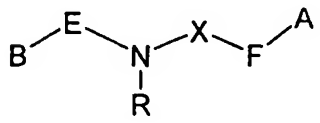
Novel Aromatic Amines and Amides Acting on the Melanocortin Receptors

The present invention relates to novel aromatic amines and amides, and to the use of these amines and amides for the treatment of obesity, anorexia, inflammation, mental disorders and other diseases associated with the melanocortin receptors or related systems, e.g. the melanocyte stimulating hormones.

A number of large linear and cyclic peptides are known in the art which show high specific binding to melanocortin (MC) receptors. The agonistic and/or antagonistic properties of these peptides are also known. See for example "Melanocortin Receptor ligands and methods of using same" by Dooley, Girten and Houghten (WO99/21571). Two patent applications (WO99/55679 and WO99/64002) have been published which includes small molecules showing activity on the melanocortin receptors. However, the compounds in the present invention are structuarlly different from the previously published melanocortin agonists, and hence the observed effects are unexpected.

One aspect of the present invention is therefore to provide low molecular weight compounds showing activity on melanocortin receptors and which may be taken up after per oral administration and which may penetrate well through the blood brain barrier.

The present invention provides novel compounds of the general formula (I):

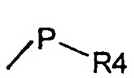


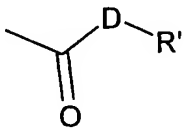
wherein X is carbonyl, methylene or is absent (i.e. a single bond)

and E and F are independently a saturated or unsaturated, straight or branched chain acyclic hydrocarbon group having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms, preferably 1, 2, 3, 4 or 5 carbon atoms; or E and/or F may be absent.

Examples of E and F include straight or branched chain alkyl and alkene groups, optionally substituted by one or more halogen atoms, preferably chlorine. Preferred examples of E and F include methyl, ethyl, propyl, iso-propyl, butyl, t-butyl, pentyl, t-pentyl, iso-pentyl, hexyl and heptyl, and the corresponding alkene groups, particularly those in which one or more of the carbon atoms involved in a double bond is substituted with chlorine.

R is selected from:





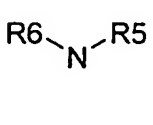
wherein P and D are independently a saturated or unsaturated, straight or branched chain acyclic hydrocarbon group having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms, preferably 1, 2, 3, 4 or 5 carbon atoms, or D may be absent (i.e. D is a single bond).

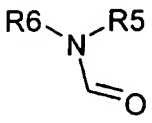
Examples of P and D include straight or branched chain alkyl and alkene groups, optionally substituted by one or more halogen atoms, preferably chlorine. Preferred examples of P and D include methyl, ethyl, propyl, iso-propyl, butyl, t-butyl, pentyl, t-pentyl, iso-pentyl, hexyl and heptyl, and the corresponding alkene groups, particularly those in which one or more of the carbon atoms involved in a double bond is substituted with chlorine.

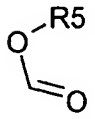
R' is a hydroxy, methyl, cyclohexyl, cyclopentyl, guanidine, aminoguanidine, or a carboxylic group.

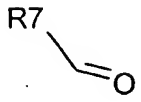
R4 is a hydroxy, cyclohexyl, cyclopentyl, guanidine, aminoguanidine, or a carboxylic group.

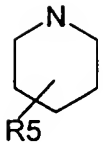
R4 or R' is also selected from:

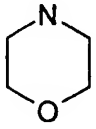








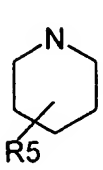


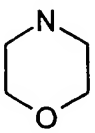


R4 may also be selected from A and B, as defined below.

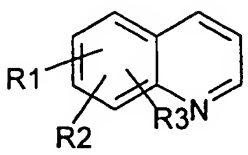
R5 and R6 are the same or different and selected from hydrogen, lower alkyl such as methyl, ethyl, propyl, iso-propyl, butyl, t-butyl, pentyl, t-pentyl, iso-pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or hexyl.

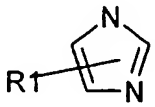
R7 is selected from:

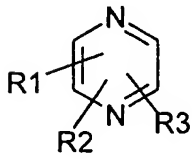


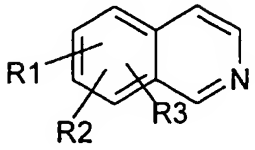


Wherein A and B are independently selected from the following:









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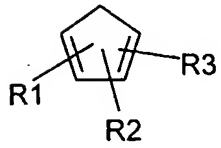
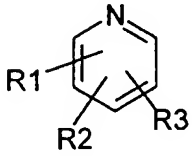
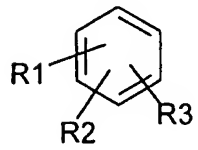
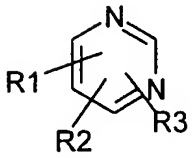
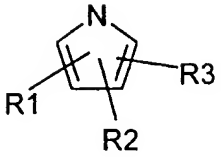
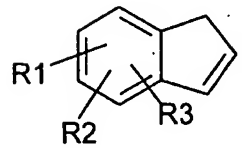


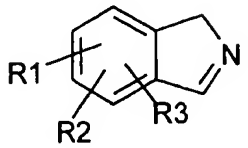


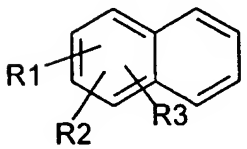


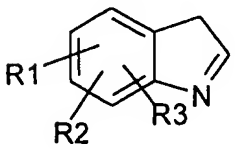






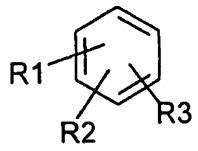


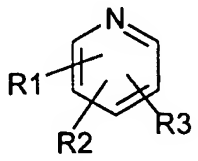


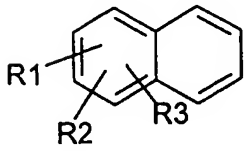


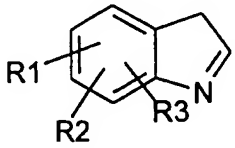
wherein R_1, R_2 and R_3 are the same or different and are selected from hydrogen, halogen, alkyl having 1 to 5 carbon atoms, electron donor groups such as alkoxy having 1-5 carbon atoms or hydroxy, electron acceptor groups selected from cyano, nitro, trifluoroalkyl or amide; and the pharmacologically active salts thereof.

Preferably, A and B are the same or different and are selected from the following:









In cases where A and/or B are bicyclic groups, it should be noted that R1, R2 and R3 represent substituents which may be present on either of the rings. Furthermore, it should be noted that A and B may be attached in the carbon backbone of the compound of general formula (I) at any suitable point within A or B, preferably at the 1, 2 or 3 position; and most preferably A and B are not attached in the carbon backbone via an N-atom in A and/or B.

When used in the foregoing definitions, the term alkyl is meant to include straight or branched chain hydrocarbon groups; the term alkoxy is meant to include straight or branched chain alkoxy groups; and the term halogen includes fluoro, chloro or bromo.

Preferably, the "alkyl having 1 to 5 carbon atoms" is a lower alkyl such as methyl, ethyl, propyl or iso-propyl.

Preferably, the "alkoxy having 1 to 5 carbon atoms" is a lower alkoxy such as methoxy, ethoxy, propoxy or iso-propoxy.

Preferably, the halogen is fluoro or chloro.

Preferably, the trifluoroalkyl is trifluoromethyl, trifluoroethyl, trifluoropropyl or trifluoroiso-propyl.

The compounds of formula (I) have basic properties and, consequently, they may be converted to their therapeutically active acid addition salts by treatment with appropriate acids, e.g. inorganic acids such as hydrochloric, hydrobromic, sulphuric, nitric and phosphoric acid, or organic acids such as acetic, propanoic, glycolic, lactic, malonic, succinic, fumaric, tartaric, citric and palmoic acid.

Conversely, the salt form may be converted into the free base form by treatment with alkali.

The present invention relates novel aromatic amines. Some of the compounds of the present invention have been biologically tested in the melanocortin system and have surprisingly been shown to be capable of binding to melanocortin receptors as well as showing activity in functional assays.

Some of the compounds of the present invention are either agonists or antagonists of a specific MC-receptor or of a number of MC-receptors, e.g. MC1, MC3, MC4 or/and MC5 receptors.

The MC-receptors belong to the class of G-protein coupled receptors which are all built from a single polypeptide forming 7 transmembrane domains. Five such receptors types, termed MC1, MC2, MC3, MC4 and MC5, have been described. The MC receptor's signaling is mainly mediated via cAMP but also other signal transduction pathways are known. They are distinctly distributed in the body.

MC-receptors are linked to a variety of physiological actions that are thought to be mediated by distinct subtypes of the MC-receptors. In many cases, however, it is not entirely clear which of the subtypes is responsible for the effect.

It has long been known that MSH-peptides may affect many different processes such as motivation, learning, memory, behaviour, inflammation, body temperature, pain perception, blood pressure, heart rate, vascular tone, brain blood flow, nerve growth, placental development, aldosterone synthesis and release, thyroxin release, spermatogenesis, ovarian weight, prolactin and FSH secretion, uterine bleeding in women, sebum and pheromone secretion, blood glucose levels, intrauterine foetal growth, as well as other events surrounding parturition (Eberle, AN: The melanotropins: Chemistry, physiology and mechanisms of action. Basel: Karger, Switzerland. 1988, ISBN 3-8055-4678-5; Gruber, and Callahan, Am. J. Physiol. 1989, 257, R681-R694; De Wildt et al., J. Cardiovascular Pharmacology. 1995, 25, 898-905), as well as inducing natriuresis (Lin et al., Hypertension. 1987, 10, 619-627).

It is also well-known that the immunomodulatory action of α-MSH includes both immuno-stimulatory and immunosuppressive effects. Several studies have shown that α-MSH antagonizes the effects of pro-inflammatory cytokines such as IL-1α, IL-1β, IL-6 and TNFα, and induces the production of the anti-inflammatory cytokine, IL-10 (for review see Catania & Lipton, 1993).

Eating behaviour is regulated by a complex network of physiological regulatory pathways that involve both the central nervous system and peripheral sites. Factors such as leptin, insulin, NPY (neuropeptide Y), orexins, CRF (Corticotropin-Releasing Factor, release hormone) and melanocortic peptides (Schwartz; Nature Medicine 1998, 4, 385-386) are known to control the amount of food intake both during short and long term, which may affect body weight, body fat mass and growth rate. Recent studies have shown a role of MC-receptors, especially the MC4 receptor, for control of food intake, and there is evidence indicating that the melanocortins and the MC4 receptor are important factors downstream of leptin. Intracerebroventricular injections of the melanocortic peptides α-MSH and

ACTH(1-24) have been shown to markedly inhibit feeding (Poggioli et al., Peptides, 1986, 7, 843-848; Vergoni et al., Neuropeptides, 1986, 7, 153-158).

The MC5-receptor has recently been attributed a role in control of exocrine gland function (van der Kraan, et al., Endocrinol. 1998, 139, 2348-2355; Chen et al., Cell. 1997, 91, 789-798).

In addition, the melanocortic peptides have distinct effects on sexual functions in that they cause erection in males (Donovan, Psychol. Med. 1978, 8, 305-316), presumably mediated by a central agonistic effect of the peptide on MC-receptors. It has also been shown that a MC-receptor blocker could inhibit the erectogenic effect of melanocortic peptides (Vergoni et al., Eur. J. Pharmacol, 1998, 362; 95-101).

Some of the compounds of formula (I) and/or their pharmaceutically acceptable salts have valuable pharmacological properties, making them useful for the treatment of mental disorders such as psychoses, depression, anxiety, senile dementia, Alzheimer's disease, drug abuse disorders and eating disorders such as anorexia and bulimia.

Some of the compounds of formula (I) and/or their pharmaceutically acceptable salts have valuable pharmacological properties, making them useful for the treatment of dysfunctions of the endocrine system and other hormonal systems such as excessive menstruations, endometriosis, events related to parturition, dysfunctions related to prolactin, dysfunctions related to growth hormone, dysfunctions related to testosterone, dysfunctions related to estrogen, dysfunctions related to glucocorticoids, dysfunctions related to luteinizing hormone and follicle stimulating hormone, inducing abortion, for prevention of abortion and/or for treatment of events related to parturition.

Others of the compounds of formula (I) and/or their pharmaceutically acceptable salts have valuable pharmacological properties, making them useful for the

treatment of sexual functions / dysfunctions such as inducing erection in man. to induce erection in animal breeding, to stimulate intercourse in animals which are difficult to mate, in particular rare species or valuable strains, pets. cats, dogs. horses or to reduce sexual behaviour in animals, e.g. for pets, cats etc., to treat impotence and disorders related to sexual drive, including lack of sexual drive or abnormal sexual drive in both men and women.

Some of the compounds of formula (I) and/or their pharmaceutically acceptable salts have valuable pharmacological properties, making them useful for the treatment of inflammation such as inflammations related to the production of nitric oxide, inflammation related to increased amounts (upregulated amounts) of inducible nitric oxide synthase, inflammation related to activation of transcriptional activators, inflammation related to nuclear factor kappa beta, inflammation related to macrophages, neutrophils, monocytes, keratinocytes, fibroblasts, melanocytes, pigment cells and endothelial cells, inflammation related to increased production and/or release of inflammatory cytokines, such as e.g. interleukins, in particular interleukin 1 (IL-1), interleukin 6 (IL-6) and tumor necrosis factor α (TNF-α).

In the present specification, "increased production" refers to increased formation, increased release, or increased amount of an endogenous compound locally, regionally or systemically in a patient compared to the amount of said endogenous compound in a healthy individual. In the present specification, "upregulated" refers to an increased activity or amount of the compound compared with that in a healthy individual.

In the present specification, "decreased production" refers to decreased formation, decreased release, or decreased amount of an endogenous compound in a patient compared to the amount of said endogenous compound in a healthy individual. In the present specification, "downregulated" refers to a decreased activity or amount of the compound compared with that in a healthy individual.

In particular, positive treatment effects or preventive effects may be seen in conditions where inflammation or an inflammatory-like condition is caused by or being associated

with one or more of the following: allergy, hypersensitivity, bacterial infection, viral infection, inflammation caused by toxic agent, fever, autoimmune disease, radiation damage by any source including UV-radiation, X-ray radiation, γ -radiation, α- or β-particles, sun burns, elevated temperature or mechanical injury. Moreover, inflammation due to hypoxia, which is optionally followed by reoxygenation of the hypoxic area, is typically followed by severe inflammation, which condition may be positively affected by treatment with a compound of the invention.

In very specific embodiments of the invention, a compound of the invention may be administered for the prevention or therapeutic treatment of inflammatory diseases of the skin (including the dermis and epidermis) of any origin, including skin diseases having an inflammatory component. Specific examples of this embodiment of the invention include treatment of contact dermatitis of the skin, sunburns of the skin, burns of any cause, and inflammation of the skin caused by chemical agents, psoriasis, vasculitis, pyoderma gangrenosum, discoid lupus erythematosus, eczema, pustulosis palmo-plantaris, and phemphigus vulgaris.

Also comprised by the invention is the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of an inflammatory disease in the abdomen, including an abdominal disease having an inflammatory component. Specific examples of the treatment of such a disease with a compound of the invention are gastritis, including one of unknown origin, gastritis perniciosa (atrophic gastritis), ulcerous colitis (colitis ulcerosa), morbus Crohn, systemic sclerosis, ulcus duodeni, coeliac disease, oesophagitis and ulcus ventriculi.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of systemic or general and/or local immunological diseases, including those of an autoimmune nature, and other inflammatory diseases of a general nature. Specific examples include treatment of rheumatoid arthritis, psoriatic arthritis, systemic sclerosis, polymyalgia rheumatica, Wegener's granulomatosis, sarcoidosis, eosinophilic fasceitis, reactive arthritis, Bechterew's disease, systemic lupus erythematosus, arteritis temporalis, Behcet's

disease, morbus Burger, Good Pastures' syndrome, eosinophilic granuloma, fibromyalgia, myositis, and mixed connective tissue disease. Included therein is also arthritis, including arthritis of unknown origin.

Further included in the invention is administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of a disease of the peripheral and/or central nervous system related to inflammation. Included in this aspect of the invention is the treatment of cerebral vasculitis, multiple sclerosis, autoimmune ophthalmitis and polyneuropathia. Comprised by the invention is also the administration of a compound of the invention for the treatment of an inflammation of the central nervous system to prevent apoptotic cell death. Moreover, as some of the compounds of the invention show a distinct ability to induce nerve regeneration, positive treatment effects are often seen in central nervous system diseases involving damage of cells in this region. This aspect of the invention also includes treatment of traumatic injuries to the central nervous system, brain edema, multiple sclerosis, Alzheimer's disease, bacterial and viral infections in the central nervous system, stroke, and haemorrhagia in the central nervous system.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases of the eye and tear glands related to inflammation. Specific examples of such diseases comprise anterior and posterior uveitis, retinal vasculitis, optic neuritis, optic neuromyelitis, Wegener's granulomatosis, Sjögren's syndrome, episcleritis, scleritis, sarcoidosis affecting the eye and polychondritis affecting the eye.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases of the ear related to inflammation, specific examples of which include polychondritis affecting the ear and external otitis.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases of the nose

related to inflammation, specific examples of which are sarcoidosis, polychondritis and mid-line granuloma of the nose.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to inflammation of the mouth, pharynx and salivary glands. Specific examples include Wegener's granulomatosis, mid-line granuloma, Sjögren's syndrome and polychondritis in these areas.

Included in the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to inflammation in the lung. Specific examples include treatment of idiopathic alveolitis, primary pulmonary hypertension, bronchitis, chronic bronchitis, sarcoidosis, alveolitis in inflammatory systemic disease, pulmonary hypertension in inflammatory systemic disease, Wegener's granulomatosis and Good Pastures' syndrome.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to the inflammation of the heart. Specific examples include treatment of pericarditis, idiopathic pericarditis, myocarditis, Takayasus' arteritis, Kawasaki's disease, coronary artery vasculitis, pericarditis in inflammatory systemic disease, myocarditis in inflammatory systemic disease, endocarditis and endocarditis in inflammatory systemic disease.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to inflammation of the liver. Specific examples include treatment of hepatitis, chronic active hepatitis, biliary cirrhosis, hepatic damage by toxic agents, interferon induced hepatitis, hepatitis induced by viral infection, liver damage induced by anoxia and liver damage caused by mechanical trauma.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to inflammation of the pancreas. Specific examples include treatment (and prevention) of diabetes mellitus, acute pancreatitis and chronic pancreatitis.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to the inflammation of the thyroidea. Specific examples of these embodiments of the invention include treatment of thyreoiditis, autoimmune thyreoiditis and Hashimoto's thyreoiditis.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to inflammation of the kidney. Specific examples include treatment of glomerulonephritis, glomerulonephritis in systemic lupus erythematosus, periarteritis nodosa, Wegener's granulomatosis, Good-Pastures' syndrome, HLAb27 associated diseases, IgA nephritis (IgA = Immunoglobulin A), pyelonephritis. chronic pyelonephritis and interstitial nephritis.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to the inflammation of the joints. Specific examples include treatment of Bechterew's disease, psoriatic arthritis, rheumatoid arthritis, arthritis in colitis ulcerosa, arthritis in morbus Crohn, affection of joints in systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease, reactive arthritis, Reiter's syndrome. Moreover, included in this embodiment of the invention is treatment of arthrosis of any joint, in particular arthrosis of finger joints, the knee and the hip.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of diseases related to the inflammation of blood vessels. Specific examples include treatment of arteritis temporalis, periarteritis nodosa, arteriosclerosis, Takayasus' arteritis and Kawasaki's

disease. Particularly advantageous is the capacity of some compounds of the invention to afford protection against and prevention of arteriosclerosis. This is in part due to the capacity of some compounds of formula (I) or the pharmacologically acceptable salts thereof to prevent the induction of inducible nitric oxide synthesis (iNOS) caused by the action of oxidized Low Density Lipoprotein on endothelial cells and blood vessel walls.

Comprised by the invention is also the administration of a compound of the invention for the treatment of drug-induced disorders of the blood and lymphoid system, including the treatment of drug-induced hypersensitivity (including drug hypersensitivity) affecting blood cells and blood cell forming organs (e.g. bone marrow and lymphoid tissue). Specific embodiments of this aspect of the invention include the treatment of anemia, granulocytopenia, thrombocytopenia, leukopenia, aplastic anemia, autoimmune hemolytic anemia, autoimmune thrombocytopenia and autoimmune granulocytopenia.

The compounds of the invention may also be administered for the treatment of fast allergic disorders (Type I allergy). Included in this embodiment of the invention is the treatment of anaphylactic reactions, anaphylactoid reactions, asthma, asthma of allergic type, asthma of unknown origin, rhinitis, hay fever and pollen allergy.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of inflammation related to infections of any origin. Specific examples include treatment of inflammation secondary to infection caused by virus, bacteria, helminths and protozoae.

Comprised by the invention is also the administration of a compound of formula (I) or a pharmacologically acceptable salt thereof for the treatment of inflammations related to trauma and/or tissue injury of any origin.

Some of the compounds of formula (I) or pharmaceutically acceptable salts thereof have valuable pharmacological properties, making them useful for the treatment of

disorders of the cardiovascular system such as disorders related to blood pressure, heart rate, vascular tone, natriuresis, bleeding, shock, disorders related to ischemia, infarction, repercussion injuries, arrhythmias of the heart, in particular during ischemia, or for the treatment of arrhythmias associated with reoxygenation of a previously ischemic period of the heart.

Some of the compounds of formula (I) or the pharmaceutically acceptable salts thereof have valuable pharmacological properties, making them useful for the treatment of pain such as pain of central origin, pain seen after damage to the CNS, stroke, infarction, pain of peripheral origin, chronic pain, neuropathies and disorders where a treatment effect is achieved by stimulation of receptors in the periaqueductal grey area.

Because of the capacity of some of the compounds of the invention to stimulate pigment formation in epidermal cells, some of the compounds of the invention may be also useful for inducing skin tanning for cosmetic reasons, for treatment of vitiligo, or any other condition where darkening of skin color is desired. Moreover, because of the ability of some of the compounds of the invention to inhibit pigment formation in cells of the skin, they may also be useful for inducing lighter skin color for cosmetic reasons, or during any condition where a lighter color of skin is desired.

Some of the compounds of formula (I) or the pharmaceutically acceptable salts thereof have valuable pharmacological properties, making them useful to cause skin tanning, darkening the colour of the skin, to induce melanin synthesis in the skin, to reduce skin tanning, lightening the colour of the skin, to reduce or block melanin synthesis in the skin, to cause anti-inflammatory actions in the skin, to modulate epidermal growth, to improve wound healing, to treat acne, seborrhoea, acne roseacea, conditions related to malfunctions of the glands of the skin, e.g. sebacous glands and over or underproduction of sebum.

Some of the compounds of the invention are useful for inhibiting or stimulating the *in vivo* formation of second messenger elements such as cAMP. Such

inhibition/stimulation may be used in cells or crushed cell systems *in vitro*, e.g. for analytical or diagnostic purposes.

For analytical and diagnostic purposes the compounds of the invention may be used in radioactive form where they comprise one or more radioactive labels or gamma or positron emitting isotopes, to be used in radioligand binding for the quantification as well as tissue localisation of MC-receptors, for analysis of dissociation/association constants, and for imaging of in vivo binding by the use of scintigraphy, positron emission tomography (PET) or single photon emission computed tomography (SPECT), or for the diagnosis of disease and treatment of any malignancy where the malignant cells contain MC receptors.

Alternatively the compounds of the invention can be labelled with any other type of label that allows detection of the respective compound, e.g. fluorescence, biotin, or labels activated by gamma-irradiation, light photons or biochemical processes, or by light or UV-light (the latter in order to obtain a compound useful for covalent labelling of MC receptors by a photoaffinity technique).

Some of the compounds of formula (I) or the pharmacologically acceptable salts thereof may also be tagged with a toxic agent (i.e. doxorubicin, ricin, diphtheria toxin or other) and used for targeted delivery to malignant cells bearing MC receptors, or tagged with a compound capable of activating the endogenous immune system for triggering the immune system (for example a compound, monoclonal antibody or other, capable of binding to a T-cell antigen, e.g. CD3 or other) for treatment of malignancies and other MC receptor expressing diseases. The thus formed hybrid compound will direct cytotoxic cells to the malignant melanoma cells or the MC1-receptor bearing malignant cells and inhibit the tumor growth.

Some of the compounds of formula (I) or a pharmacologically acceptable salt thereof may be attached to the antibody chemically by covalent or non-covalent bond(s).

Some of the compounds of the invention may be used for the treatment and diagnosis of diseases, disorders and/or pathological conditions in an animal, in particular in man.

The present invention also relates to a pro-drug which, upon administration to an animal or a human, is converted to a compound of the invention. Pro-drugs of the compounds of formula (I) and their pharmacologically acceptable salts may be used for the same purposes as described in this specification for the compounds of the invention, as well as is disclosed in the Examples given below.

The compounds of the present invention may be bound covalently or non-covalently to one or several of other molecule(s) of any desired structure(s); the thus formed modified compound or complex may be used for the same purposes as described in this specification for the compounds of the invention, as well as is disclosed in the Examples given below. In a particularly important embodiment of the invention, a radioactively-labeled molecule is covalently bound to a compound of formula (I) or a pharmacologically acceptable salt thereof so as to make a compound of formula (I) or a pharmacologically acceptable salt thereof radioactively labeled.

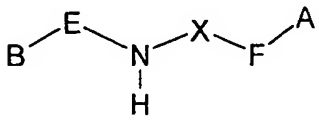
The invention also relates to methods for the manufacture and pharmaceutical preparations comprising one or more of the compounds of the invention, as well as to their uses for various medical and veterinary practices related to melanocyte stimulating hormone receptors.

Some of the compounds of the invention bind to one or more MC-receptors. By the term "bind to one or more MC-receptors" is in this context intended a capacity of the compound of the invention to compete for the binding of [125-I]NDP-MSH at an MC-receptor, the MC-receptor preferably being one selected from the MC1, MC3, MC4 and/or MC5-receptors, using a binding assay such as that described in Example 6. In a further meaning, the term "bind to one or more MC-receptors" is in this context intended that the Ki-value of the compound of the invention, determined using a method such as that described in Example 6, is less than 1,000,000 nM, preferably less than 100,000 nM, more preferably less than 10,000 nM, somewhat

more preferably less than 1,000 nM, even somewhat preferably less than 100 nM, and most preferably less than 50 nM. Most preferably, the compound of the invention has a Ki of less than 1,000 nM or less than 50 nM for a melanocortin receptor.

The compounds having the general formula (I) may be prepared by the following methods.

Method 1.



(II)

(III)

A compound of formula (III), wherein R is as previously defined and Y is a suitable leaving group such as halogen, alkyl- or arylsulfonate is reacted with a compound of formula (II), wherein A, B, E, F and X are as previously defined. The reactions may be carried out using standard N-alkylation procedures.

Legends to the Figures

Figures 1-2 Effect of Compound 2:1 on paw oedema and total number of white blood cells in mice

Examples

The following examples are intended to illustrate but not to limit the scope of the invention, although the compounds named are of particular interest for the intended purposes. These compounds have been designated by a number code, a:b, where a means the number of the example, wherein the preparation of the compound is described, and b refers to the order of the compound prepared according to that example. Thus example 1:2 means the second compound prepared according to example 1.

The structures of the compounds were confirmed by IR, NMR, MS and elementary analysis. When melting points are given, these are uncorrected.

Example 1:1.

N-Benzyl-N-(4-guanidino-butyl)-2-(1H-indol)-3-yl)-acetamide hydrochloride

N-(4-Benzylamino-butyl)-N',N''-bis-(benzyloxycarbonyl)-guanidine

To a solution of 4-N-benzylbutylguanidine (1.78g, 10mmol) in acetonitrile (15ml) under stirring was added 1,3-bis-(benzyloxycarbonyl)-2-methylthiopseudourea (3.58g, 10mmol). Stirring was continued for 24h at room temperature, the reaction mixture concentrated in vacuo, purified by chromatography (silica gel; ethylacetate) to give viscous oil (4.38g, 90%).

N-Benzyl-N-(4-guanidino-butyl)-2-(1H-indol)-3-yl)-acetamide hydrochloride

To a solution of N-(4-benzylamino-butyl)-N',N''-bis-(benzyloxycarbonyl)-guanidine (0.24g, 0.5mmol) and 3-(1H-Indol-3-yl)-propionic acid 2,5-dioxo-pyrrolidin-1-yl ester (0.14g, 0.5mmol) in acetonitrile (10ml) under stirring saturated $NaHCO_3$ solution until pH9 was added, stirred for 2 days at room

temperature, evaporated in vacuo. The residue was dissolved in ethylacetate (12ml), washed with water (2x5ml), dried ($MgSO_4$) and evaporated in vacuo. To a crude intermediate dissolved in ethanol (10ml), 5% Pd/C (20mg) and 4 drops of concd HCl were added and hydrogenated for 1h at ambient pressure, the Pd catalyst was filtered off, the solution evaporated in vacuo, and the residue purified by chromatography (silica gel; chloroform-methanol-water, 120:20:1) to give the title product (0.10g, 47%) as a colourless foam: m.p. 100-105^{0}C. ^{1}H NMR (DMSO-D6), δ: 1.21-1.68 (4H, m); 2.90-3.39 (4H, m, overlapped with HOD); 3.73 and 3.84 (2H, s and s); 4.52 and 4.64 (2H, s and s); 6.83-7.96 (15H, m); 10.92 ppm (1H, s). Anal. Calcd for $C_{22}H_{27}N_5O$*HCl*0.7H_2O: C 62.0; H 6.9; N 16.4. Found: C 62.1; H 6.8; N 16.5.

The following compounds were made in similar manner to the above:

Number	Compound
1:1	N-Benzyl-N-(4-guanidino-butyl)-2-(1H-indol)-3-yl)-acetamide, hydrochloride 0.7 hydrate m.p. 100-105°C
1:2	N-Benzyl-N-(4-guanidino-butyl)-4-(1H-indol-3-yl)-butyramide, hydrochloride hydrate m.p. 82-87°C
1:3	1H-Indole-3-carboxylic acid (2-amino-ethyl)-naphthalen-2-ylmethyl-amide
1:4	N-(2-Amino-ethyl)-2-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-acetamide
1:5	1H-Indole-5-carboxylic acid (2-amino-ethyl)-naphthalen-2-ylmethyl-amide
1:6	N-(2-Amino-ethyl)-2-(1H-indol-3-yl)-N-(1-naphthalen-2-yl-ethyl)-acetamide
1:7	N-(2-Amino-ethyl)-2-(1H-indol-3-yl)-N-(1,2,3,4-tetrahydro-naphthalen-2-yl)-acetamide
1:8	N-(2-Amino-ethyl)-2-naphthalen-2-yl-N-(1,2,3,4-tetrahydro-naphthalen-2-yl)-acetamide

1:9 N-(3-Amino-propyl)-2-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-acetamide

1:10 N-(3-Amino-propyl)-2-naphthalen-2-yl-N-naphthalen-2-ylmethyl-acetamide

1:11 N-(3-Amino-propyl)-2-(1H-indol-3-yl)-N-(3-phenyl-allyl)-acetamide

1:12 N-(3-Amino-propyl)-2-(1H-indol-3-yl)-2-oxo-N-(3-phenyl-allyl)-acetamide

1:13 1H-Indole-5-carboxylic acid (3-amino-propyl)-(3-phenyl-allyl)-amide

1:14 N-(3-Amino-propyl)-N-(2-chloro-3-phenyl-allyl)-2-(1H-indol-3-yl)-2-oxo-acetamide

1:15 1H-Indole-3-carboxylic acid (3-amino-propyl)-(2-methyl-3-phenyl-allyl)-amide

1:16 N-(3-Amino-propyl)-2-(1H-indol-3-yl)-N-(2-methyl-3-phenyl-allyl)-acetamide

1:17 N-(3-Amino-propyl)-2-(1H-indol-3-yl)-N-(2-methyl-3-phenyl-allyl)-2-oxo-acetamide

1:18 1H-Indole-3-carboxylic acid (3-amino-propyl)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amide

1:19 N-(3-Amino-propyl)-2-(1H-indol-3-yl)-N-(1,2,3,4-tetrahydro-naphthalen-2-yl)-acetamide

1:20 1H-Indole-5-carboxylic acid (3-amino-propyl)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amide

1:21 N-(3-Amino-propyl)-3-(1H-indol-3-yl)-N-(1,2,3,4-tetrahydro-naphthalen-2-yl)-propionamide

1:22 1H-Indole-3-carboxylic acid (4-amino-butyl)-naphthalen-2-ylmethyl-amide

1:23 N-(4-Amino-butyl)-2-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-acetamide

1:24 1H-Indole-5-carboxylic acid (4-amino-butyl)-naphthalen-2-ylmethyl-amide

1:25 N-(5-Amino-pentyl)-2-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-acetamide

1:26 N-(5-Amino-pentyl)-3-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-propionamide

1:27 N-(5-Amino-pentyl)-4-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-butyramide

1:28 N-[5-(4-Hydroxy-benzylamino)-pentyl]-4-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-butyramide

1:29 N-(5-Amino-pentyl)-2-(1H-indol-3-yl)-N-(1-naphthalen-2-yl-ethyl)-acetamide

1:30 N-(5-Amino-pentyl)-2-(1H-indol-3-yl)-N-[1-(4-trifluoromethyl-phenyl)-ethyl]-acetamide

1:31 N-(5-Amino-pentyl)-N-cycloheptyl-2-(1H-indol-3-yl)-acetamide

1:32 N-(5-Amino-pentyl)-N-benzo[1,3]dioxol-5-ylmethyl-4-(1H-indol-3-yl)-butyramide

1:33 N-(5-Amino-pentyl)-4-(1H-indol-3-yl)-N-(3-naphthalen-2-yl-allyl)-butyramide

1:34 N-(5-Amino-pentyl)-N-(2-chloro-3-phenyl-allyl)-4-(1H-indol-3-yl)-butyramide

1:35 N-(5-Amino-pentyl)-N-(2-chloro-3-phenyl-allyl)-3-(1H-indol-3-yl)-acrylamide

1:36 N-(5-Amino-pentyl)-4-(1H-indol-3-yl)-N-(2-methyl-3-phenyl-allyl)-butyramide

1:37 N-(5-Amino-pentyl)-3-(1H-indol-3-yl)-N-(2-methyl-3-phenyl-allyl)-acrylamide

1:38 N-(5-Amino-pentyl)-N-(4-diethylamino-benzyl)-4-(1H-indol-3-yl)-butyramide

1:39 N-(8-Amino-octyl)-3-(1H-indol-3-yl)-N-(3-phenyl-allyl)-propionamide

1:40 N-(2-Amino-ethyl)-3-(1H-indol-3-yl)-N-(3-phenyl-propyl)-propionamide

1:41 N-(3-Amino-propyl)-4-(1H-indol-3-yl)-N-phenethyl-butyramide

1:42 N-(3-Amino-propyl)-2-(1H-indol-3-yl)-N-(3-phenyl-propyl)-acetamide

1:43 N-(4-Amino-butyl)-3-(1H-indol-3-yl)-N-(3-phenyl-propyl)-propionamide

1:44 N-(5-Amino-pentyl)-2-(1H-indol-3-yl)-N-(3-phenyl-propyl)-acetamide

1:45 N-(5-Amino-pentyl)-4-(1H-indol-3-yl)-N-(3-phenyl-propyl)-butyramide

1:46 N-[4-(4-Amino-cyclohexylmethyl)-cyclohexyl]-4-(1H-indol-3-yl)-N-(3-phenyl-allyl)-butyramide

1:47 N-[4-(4-Amino-cyclohexylmethyl)-cyclohexyl]-N-benzyl-4-(1H-indol-3-yl)-butyramide

1:48 4-(1H-Indol-3-yl)-butan-2-one; compound with N1-(3-phenyl-allyl)-ethane-1,2-diamine

1:49 N-(3-Amino-propyl)-3-(1H-indol-3-yl)-N-(3-phenyl-allyl)-propionamide

1:50 N-(4-Amino-butyl)-3-(1H-indol-3-yl)-N-(3-phenyl-allyl)-propionamide

1:51 N-(5-Amino-pentyl)-3-(1H-indol-3-yl)-N-(3-phenyl-allyl)-propionamide

1:52 N-(5-Amino-pentyl)-4-(1H-indol-3-yl)-N-(3-phenyl-allyl)-butyramide

1:53 N-(3-Aminomethyl-benzyl)-4-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-butyramide

1:54 N-(3-Aminomethyl-benzyl)-N-benzyl-4-(1H-indol-3-yl)-butyramide

1:55 N-(4-Aminomethyl-benzyl)-4-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-butyramide

1:56 N-(4-Aminomethyl-benzyl)-4-(1H-indol-3-yl)-N-(3-phenyl-allyl)-butyramide

1:57 N-(2-Amino-cyclohexyl)-4-(1H-indol-3-yl)-N-(3-phenyl-allyl)-butyramide

1:58 N-(2-Guanidino-ethyl)-2-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-acetamide

1:59 N-(2-Guanidino-ethyl)-3-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-propionamide

1:60 N-(2-Guanidino-ethyl)-4-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-butyramide

1:61 N-(3-Guanidino-propyl)-2-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-acetamide

1:62 N-(3-Guanidino-propyl)-3-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-propionamide

1:63 N-(3-Guanidino-propyl)-4-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-butyramide

1:64 N-(4-Guanidino-butyl)-2-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-acetamide

1:65 N-(4-Guanidino-butyl)-3-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-propionamide

1:66 N-(4-Guanidino-butyl)-4-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-butyramide

1:67 4-(1H-Indol-3-yl)-butyric acid 3-{[(5-guanidino-pentyl)-(4-1H-indol-3-yl-butyryl)-amino]-methyl}benzylester

1:68 N-[4-(4-Guanidino-cyclohexylmethyl)-cyclohexyl]-4-(1H-indol-3-yl)-N-(3-phenyl-allyl)-butyramide

1:69 N-Benzyl-N-[4-(4-guanidino-cyclohexylmethyl)-cyclohexyl]-4-(1H-indol-3-yl)-butyramide

1:70 2-(1H-Indol-3-yl)-N-naphthalen-2-ylmethyl-N-(2-oxo-2-piperazin-1-yl-ethyl)-acetamide

1:71 2-(1H-Indol-3-yl)-N-naphthalen-2-ylmethyl-N-(3-oxo-3-piperazin-1-yl-propyl)-acetamide

Example 2:1.

[2-(1H-Indol-3-yl)-ethyl]-bis-(3-phenyl-propyl)-amine hydrochloride

Methanol saturated with dry hydrogen chloride was added to a solution of tryptamine (0.48g, 3mmol) and hydrocinnamaldehyde (0.67g, 5mmol) in methanol to reach pH 3-4. The resulting solution was cooled with ice water and treated portionwise with sodium cyanoborohydride (0.25g, 4mmol). The reaction

mixture was stirred for 24h at room temperature, keeping the pH in a range of 3-4 by the addition of hydrogen chloride solution in methanol, neutralized with saturated $NaHCO_3$ solution, evaporated and extracted with chloroform. Chloroform extracts were washed with brine, dried (Na_2SO_4), filtered and evaporated to give a pale brown semisolid, which was separated by column chromatography. Elution with chloroform afforded N-bis(3-phenylpropyl)-tryptamine. Rf=0.82 (acetonitrile-H_2O-NH_4OH, 30:2:1). The product was treated with etheral solution of hydrogen chloride, filtered, washed with ether and dried (Na_2SO_4) to give a colourless solid (0.29g, 22%): m.p. 103-106°C.

The following compounds were made in a similar manner:

Number	Compound
2:2	4-Amino-N-[2-(1H-indol-3-yl)-ethyl]-N-(4-methoxy-benzyl)-butyramide, hydrochloride m.p. foam (hygroscopic)
2:3	2-Amino-5-guanidino-pentanoic acid naphthalen-2-ylmethyl-naphthalen-1-ylmethyl-amide
2:4	2-Amino-5-guanidino-pentanoic acid [2-(1H-indol-3-yl)-ethyl]-naphthalen-2-ylmethyl-amide
2:5	2-Amino-5-guanidino-pentanoic acid (1H-indol-3-ylmethyl)-naphthalen-2-ylmethyl-amide
2:6	4-Guanidino-N-[2-(1H-Indol-3-yl)-ethyl]-N-(4-methoxy-benzyl)-butyramide, hydrochloride m.p. 172-174 °C
2:7	2-amino-N-[2-(1H-indol-3-yl)-ethyl]-N-(4-methoxy-benzyl)-acetamide hydrochloride hydrate, m.p. 140-145°C
2:8	2-amino-N-benzyl-N-[2-(1H-indol-3-yl)-ethyl]-butyramide hydrochloride hydrate, m.p. 180-182°C
2:9	3-amino-N-[2-(1H-indol-3-yl)-ethyl]-N-(6-phenyl-heptyl)-propionamide hydrochloride, m.p. hygroscopic foam
2:10	8-amino-octanoic acid [2-(1H-indol-3-yl)-ethyl]-(6-phenyl-heptyl)-amide hydrochloride, m.p. foam

2:11 8-amino-octanoic acid (7-phenyl-heptyl)-(6-phenyl-heptyl)-amide hydrochloride 1.5 hydrate, m.p. yellowish oil

The compounds given in Examples 3 to 5 were synthesized in analogy with either of the methods given in Examples 1 and 2.

Example 3

Number Compound

3:1 2-Amino-N-[4-(1H-indol-3-yl)-butyl]-N-(3,4,5-trimethoxy-benzyl)-acetamide

3:2 2-Amino-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-N-(3,4,5-trimethoxy-benzyl)-acetamide

3:3 2-Amino-N-benzo[1,3]dioxol-5-ylmethyl-N-[2-(2-methyl-1H-indol-3-yl)-ethyl]-acetamide

3:4 2-Amino-N-indan-2-yl-N-(1H-indol-3-ylmethyl)-acetamide

3:5 2-Amino-N-benzyl-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-acetamide

3:6 2-Amino-N-benzyl-N-pyridin-3-ylmethyl-acetamide

3:7 2-Amino-N-(2-chloro-6-methyl-pyridin-3-ylmethyl)-N-indan-2-yl-acetamide

3:8 2-Amino-N-benzo[1,3]dioxol-5-ylmethyl-N-pyridin-3-ylmethyl-acetamide

3:9 2-Amino-N-(2-chloro-6-methyl-pyridin-3-ylmethyl)-N-(3,4,5-trimethoxy-benzyl)-acetamide

3:10 3-Amino-N-[4-(1H-indol-3-yl)-butyl]-N-(3,4,5-trimethoxy-benzyl)-propionamide

3:11 3-Amino-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-N-(3,4,5-trimethoxy-benzyl)-propionamide

3:12 3-Amino-N-benzo[1,3]dioxol-5-ylmethyl-N-[2-(2-methyl-1H-indol-3-yl)-ethyl]-propionamide

3:13 3-Amino-N-indan-2-yl-N-(1H-indol-3-ylmethyl)-propionamide

3:14 3-Amino-N-benzyl-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-propionamide

3:15 3-Amino-N-benzyl-N-pyridin-3-ylmethyl-propionamide

3:16 3-Amino-N-(2-chloro-6-methyl-pyridin-3-ylmethyl)-N-indan-2-yl-propionamide

3:17 3-Amino-N-benzo[1,3]dioxol-5-ylmethyl-N-pyridin-3-ylmethyl-propionamide

3:18 3-Amino-N-(2-chloro-6-methyl-pyridin-3-ylmethyl)-N-(3,4,5-trimethoxy-benzyl)-propionamide

3:19 4-Amino-N-[4-(1H-indol-3-yl)-butyl]-N-(3,4,5-trimethoxy-benzyl)-butyramide

3:20 4-Amino-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-N-(3,4,5-trimethoxy-benzyl)-butyramide

3:21 4-Amino-N-benzo[1,3]dioxol-5-ylmethyl-N-[2-(2-methyl-1H-indol-3-yl)-ethyl]-butyramide

3:22 4-Amino-N-indan-2-yl-N-(1H-indol-3-ylmethyl)-butyramide

3:23 4-Amino-N-benzyl-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-butyramide

3:24 4-Amino-N-benzyl-N-pyridin-3-ylmethyl-butyramide

3:25 4-Amino-N-(2-chloro-6-methyl-pyridin-3-ylmethyl)-N-indan-2-yl-butyramide

3:26 4-Amino-N-benzo[1,3]dioxol-5-ylmethyl-N-pyridin-3-ylmethyl-butyramide

3:27 4-Amino-N-(2-chloro-6-methyl-pyridin-3-ylmethyl)-N-(3,4,5-trimethoxy-benzyl)-butyramide

3:28 2-Guanidino-N-[4-(1H-indol-3-yl)-butyl]-N-(3,4,5-trimethoxy-benzyl)-acetamide

3:29 2-Guanidino-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-N-(3,4,5-trimethoxy-benzyl)-acetamide

3:30 N-Benzo[1,3]dioxol-5-ylmethyl-2-guanidino-N-[2-(2-methyl-1H-indol-3-yl)-ethyl]-acetamide

3:31 2-Guanidino-N-indan-2-yl-N-(1H-indol-3-ylmethyl)-acetamide

3:32 N-Benzyl-2-guanidino-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-acetamide

3:33 N-Benzyl-2-guanidino-N-pyridin-3-ylmethyl-acetamide

3:34 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-2-guanidino-N-indan-2-yl-acetamide

3:35 N-Benzo[1,3]dioxol-5-ylmethyl-2-guanidino-N-pyridin-3-ylmethyl-acetamide

3:36 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-2-guanidino-N-(3,4,5-trimethoxy-benzyl)-acetamide

3:37 4-Guanidino-N-[4-(1H-indol-3-yl)-butyl]-N-(3,4,5-trimethoxy-benzyl)-butyramide

3:38 4-Guanidino-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-N-(3,4,5-trimethoxy-benzyl)-butyramide

3:39 N-Benzo[1,3]dioxol-5-ylmethyl-4-guanidino-N-[2-(2-methyl-1H-indol-3-yl)-ethyl]-butyramide

3:40 4-Guanidino-N-indan-2-yl-N-(1H-indol-3-ylmethyl)-butyramide

3:41 N-Benzyl-4-guanidino-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-butyramide

3:42 N-Benzyl-4-guanidino-N-pyridin-3-ylmethyl-butyramide

3:43 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-4-guanidino-N-indan-2-yl-butyramide

3:44 N-Benzo[1,3]dioxol-5-ylmethyl-4-guanidino-N-pyridin-3-ylmethyl-butyramide

3:45 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-4-guanidino-N-(3,4,5-trimethoxy-benzyl)-butyramide

3:46 3-Guanidino-N-[4-(1H-indol-3-yl)-butyl]-N-(3,4,5-trimethoxy-benzyl)-propionamide

3:47 3-Guanidino-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-N-(3,4,5-trimethoxy-benzyl)-propionamide

3:48 N-Benzo[1,3]dioxol-5-ylmethyl-3-guanidino-N-[2-(2-methyl-1H-indol-3-yl)-ethyl]-propionamide

3:49 3-Guanidino-N-indan-2-yl-N-(1H-indol-3-ylmethyl)-propionamide

3:50 N-Benzyl-3-guanidino-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-propionamide

3:51 N-Benzyl-3-guanidino-N-pyridin-3-ylmethyl-propionamide

3:52 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-3-guanidino-N-indan-2-yl-propionamide

3:53 N-Benzo[1,3]dioxol-5-ylmethyl-3-guanidino-N-pyridin-3-ylmethyl-propionamide

3:54 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-3-guanidino-N-(3,4,5-trimethoxy-benzyl)-propionamide

Example 4

Number	Compound
4:1	N1-[4-(1H-Indol-3-yl)-butyl]-N1-(3,4,5-trimethoxy-benzyl)-ethane-1,2-diamine
4:2	N1-[2-(5-Methoxy-2-methyl-1H-indol-3-yl)-ethyl]-N1-(3,4,5-trimethoxy-benzyl)-ethane-1,2-diamine
4:3	N1-Benzo[1,3]dioxol-5-ylmethyl-N1-[2-(2-methyl-1H-indol-3-yl)-ethyl]-ethane-1,2-diamine
4:4	N1-Indan-2-yl-N1-(1H-indol-3-ylmethyl)-ethane-1,2-diamine
4:5	N1-Benzyl-N1-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-ethane-1,2-diamine
4:6	N1-Benzyl-N1-pyridin-3-ylmethyl-ethane-1,2-diamine
4:7	N1-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-N1-indan-2-yl-ethane-1,2-diamine
4:8	N1-Benzo[1,3]dioxol-5-ylmethyl-N1-pyridin-3-ylmethyl-ethane-1,2-diamine
4:9	N1-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-N1-(3,4,5-trimethoxy-benzyl)-ethane-1,2-diamine
4:10	N1-[4-(1H-Indol-3-yl)-butyl]-N1-(3,4,5-trimethoxy-benzyl)-propane-1,3-diamine
4:11	N1-[2-(5-Methoxy-2-methyl-1H-indol-3-yl)-ethyl]-N1-(3,4,5-trimethoxy-benzyl)-propane-1,3-diamine
4:12	N1-Benzo[1,3]dioxol-5-ylmethyl-N1-[2-(2-methyl-1H-indol-3-yl)-ethyl]-propane-1,3-diamine

4:13 N1-Indan-2-yl-N1-(1H-indol-3-ylmethyl)-propane-1,3-diamine

4:14 N1-Benzyl-N1-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-propane-1,3-diamine

4:15 N1-Benzyl-N1-pyridin-3-ylmethyl-propane-1,3-diamine

4:16 N1-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-N1-indan-2-yl-propane-1,3-diamine

4:17 N1-Benzo[1,3]dioxol-5-ylmethyl-N1-pyridin-3-ylmethyl-propane-1,3-diamine

4:18 N1-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-N1-(3,4,5-trimethoxy-benzyl)-propane-1,3-diamine

4:19 N1-[4-(1H-Indol-3-yl)-butyl]-N1-(3,4,5-trimethoxy-benzyl)-butane-1,4-diamine

4:20 N1-[2-(5-Methoxy-2-methyl-1H-indol-3-yl)-ethyl]-N1-(3,4,5-trimethoxy-benzyl)-butane-1,4-diamine

4:21 N1-Benzo[1,3]dioxol-5-ylmethyl-N1-[2-(2-methyl-1H-indol-3-yl)-ethyl]-butane-1,4-diamine

4:22 N1-Indan-2-yl-N1-(1H-indol-3-ylmethyl)-butane-1,4-diamine

4:23 N1-Benzyl-N1-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-butane-1,4-diamine

4:24 N1-Benzyl-N1-pyridin-3-ylmethyl-butane-1,4-diamine

4:25 N1-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-N1-indan-2-yl-butane-1,4-diamine

4:26 N1-Benzo[1,3]dioxol-5-ylmethyl-N1-pyridin-3-ylmethyl-butane-1,4-diamine

4:27 N1-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-N1-(3,4,5-trimethoxy-benzyl)-butane-1,4-diamine

4:28 N-{2-[[4-(1H-Indol-3-yl)-butyl]-(3,4,5-trimethoxy-benzyl)-amino]-ethyl}-guanidine

4:29 N-{2-[[2-(5-Methoxy-2-methyl-1H-indol-3-yl)-ethyl]-(3,4,5-trimethoxy-benzyl)-amino]-ethyl}-guanidine

4:30 N-(2-{Benzo[1,3]dioxol-5-ylmethyl-[2-(2-methyl-1H-indol-3-yl)-ethyl]-amino}-ethyl)-guanidine

4:31 N-{2-[Indan-2-yl-(1H-indol-3-ylmethyl)-amino]-ethyl}-guanidine

4:32 N-(2-{Benzyl-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-amino}-ethyl)-guanidine

4:33 N-[2-(Benzyl-pyridin-3-ylmethyl-amino)-ethyl]-guanidine

4:34 N-{2-[(2-Chloro-6-methyl-pyridin-3-ylmethyl)-indan-2-yl-amino]-ethyl}-guanidine

4:35 N-[2-(Benzo[1,3]dioxol-5-ylmethyl-pyridin-3-ylmethyl-amino)-ethyl]-guanidine

4:36 N-{2-[(2-Chloro-6-methyl-pyridin-3-ylmethyl)-(3,4,5-trimethoxy-benzyl)-amino]-ethyl}-guanidine

4:37 N-{4-[[4-(1H-Indol-3-yl)-butyl]-(3,4,5-trimethoxy-benzyl)-amino]-butyl}-guanidine

4:38 N-{4-[[2-(5-Methoxy-2-methyl-1H-indol-3-yl)-ethyl]-(3,4,5-trimethoxy-benzyl)-amino]-butyl}-guanidine

4:39 N-(4-{Benzo[1,3]dioxol-5-ylmethyl-[2-(2-methyl-1H-indol-3-yl)-ethyl]-amino}-butyl)-guanidine

4:40 N-{4-[Indan-2-yl-(1H-indol-3-ylmethyl)-amino]-butyl}-guanidine

4:41 N-(4-{Benzyl-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-amino}-butyl)-guanidine

4:42 N-[4-(Benzyl-pyridin-3-ylmethyl-amino)-butyl]-guanidine

4:43 N-{4-[(2-Chloro-6-methyl-pyridin-3-ylmethyl)-indan-2-yl-amino]-butyl}-guanidine

4:44 N-[4-(Benzo[1,3]dioxol-5-ylmethyl-pyridin-3-ylmethyl-amino)-butyl]-guanidine

4:45 N-{4-[(2-Chloro-6-methyl-pyridin-3-ylmethyl)-(3,4,5-trimethoxy-benzyl)-amino]-butyl}-guanidine

4:46 N-{3-[[4-(1H-Indol-3-yl)-butyl]-(3,4,5-trimethoxy-benzyl)-amino]-propyl}-guanidine

4:47 N-{3-[[2-(5-Methoxy-2-methyl-1H-indol-3-yl)-ethyl]-(3,4,5-trimethoxy-benzyl)-amino]-propyl}-guanidine

4:48 N-(3-{Benzo[1,3]dioxol-5-ylmethyl-[2-(2-methyl-1H-indol-3-yl)-ethyl]-amino}-propyl)-guanidine

4:49 N-{3-[Indan-2-yl-(1H-indol-3-ylmethyl)-amino]-propyl}-guanidine

4:50 N-(3-{Benzyl-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-amino}-propyl)-guanidine

4:51 N-[3-(Benzyl-pyridin-3-ylmethyl-amino)-propyl]-guanidine

4:52 N-{3-[(2-Chloro-6-methyl-pyridin-3-ylmethyl)-indan-2-yl-amino]-propyl}-guanidine

4:53 N-[3-(Benzo[1,3]dioxol-5-ylmethyl-pyridin-3-ylmethyl-amino)-propyl]-guanidine

4:54 N-{3-[(2-Chloro-6-methyl-pyridin-3-ylmethyl)-(3,4,5-trimethoxy-benzyl)-amino]-propyl}-guanidine

Example 5

Number Compound

5:1 2,3,4-Trihydroxy-N-[4-(1H-indol-3-yl)-butyl]-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:2 2,3,4-Trihydroxy-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:3 N-Benzo[1,3]dioxol-5-ylmethyl-2,3,4-trihydroxy-N-[2-(2-methyl-1H-indol-3-yl)-ethyl]-benzamide

5:4 2,3,4-Trihydroxy-N-indan-2-yl-N-(1H-indol-3-ylmethyl)-benzamide

5:5 N-Benzyl-2,3,4-trihydroxy-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-benzamide

5:6 3-Dimethylamino-N-[4-(1H-indol-3-yl)-butyl]-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:7 3-Dimethylamino-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:8 N-Benzo[1,3]dioxol-5-ylmethyl-3-dimethylamino-N-[2-(2-methyl-1H-indol-3-yl)-ethyl]-benzamide

5:9 3-Dimethylamino-N-indan-2-yl-N-(1H-indol-3-ylmethyl)-benzamide

5:10 N-Benzyl-3-dimethylamino-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-benzamide

5:11 4-Ethoxy-N-[4-(1H-indol-3-yl)-butyl]-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:12 4-Ethoxy-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:13 N-Benzo[1,3]dioxol-5-ylmethyl-4-ethoxy-N-[2-(2-methyl-1H-indol-3-yl)-ethyl]-benzamide

5:14 4-Ethoxy-N-indan-2-yl-N-(1H-indol-3-ylmethyl)-benzamide

5:15 N-Benzyl-4-ethoxy-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-benzamide

5:16 2-Hydroxy-N-[4-(1H-indol-3-yl)-butyl]-6-isopropyl-3-methyl-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:17 2-Hydroxy-6-isopropyl-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-3-methyl-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:18 N-Benzo[1,3]dioxol-5-ylmethyl-2-hydroxy-6-isopropyl-3-methyl-N-[2-(2-methyl-1H-indol-3-yl)-ethyl]-benzamide

5:19 2-Hydroxy-N-indan-2-yl-N-(1H-indol-3-ylmethyl)-6-isopropyl-3-methyl-benzamide

5:20 N-Benzyl-2-hydroxy-6-isopropyl-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-3-methyl-benzamide

5:21 2-Fluoro-N-[4-(1H-indol-3-yl)-butyl]-5-methyl-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:22 2-Fluoro-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-5-methyl-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:23 N-Benzo[1,3]dioxol-5-ylmethyl-2-fluoro-5-methyl-N-[2-(2-methyl-1H-indol-3-yl)-ethyl]-benzamide

5:24 2-Fluoro-N-indan-2-yl-N-(1H-indol-3-ylmethyl)-5-methyl-benzamide

5:25 N-Benzyl-2-fluoro-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-5-methyl-benzamide

5:26 N-Benzyl-2,3,4-trihydroxy-N-pyridin-3-ylmethyl-benzamide

5:27 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-2,3,4-trihydroxy-N-indan-2-yl-benzamide

5:28 N-Benzo[1,3]dioxol-5-ylmethyl-2,3,4-trihydroxy-N-pyridin-3-

ylmethyl-benzamide

5:29 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-2,3,4-trihydroxy-N-(3,4.5-trimethoxy-benzyl)-benzamide

5:30 N-Benzyl-3-dimethylamino-N-pyridin-3-ylmethyl-benzamide

5:31 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-3-dimethylamino-N-indan-2-yl-benzamide

5:32 N-Benzo[1,3]dioxol-5-ylmethyl-3-dimethylamino-N-pyridin-3-ylmethyl-benzamide

5:33 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-3-dimethylamino-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:34 N-Benzyl-4-ethoxy-N-pyridin-3-ylmethyl-benzamide

5:35 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-4-ethoxy-N-indan-2-yl-benzamide

5:36 N-Benzo[1,3]dioxol-5-ylmethyl-4-ethoxy-N-pyridin-3-ylmethyl-benzamide

5:37 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-4-ethoxy-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:38 N-Benzyl-2-hydroxy-6-isopropyl-3-methyl-N-pyridin-3-ylmethyl-benzamide

5:39 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-2-hydroxy-N-indan-2-yl-6-isopropyl-3-methyl-benzamide

5:40 N-Benzo[1,3]dioxol-5-ylmethyl-2-hydroxy-6-isopropyl-3-methyl-N-pyridin-3-ylmethyl-benzamide

5:41 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-2-hydroxy-6-isopropyl-3-methyl-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:42 N-Benzyl-2-fluoro-5-methyl-N-pyridin-3-ylmethyl-benzamide

5:43 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-2-fluoro-N-indan-2-yl-5-methyl-benzamide

5:44 N-Benzo[1,3]dioxol-5-ylmethyl-2-fluoro-5-methyl-N-pyridin-3-ylmethyl-benzamide

5:45 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-2-fluoro-5-methyl-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:46 N-Benzyl-N-pyridin-3-ylmethyl-4-[(thiophen-2-ylmethylene)-amino]-benzamide

5:47 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-N-indan-2-yl-4-[(thiophen-2-ylmethylene)-amino]-benzamide

5:48 N-Benzo[1,3]dioxol-5-ylmethyl-N-pyridin-3-ylmethyl-4-[(thiophen-2-ylmethylene)-amino]-benzamide

5:49 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-4-[(thiophen-2-ylmethylene)-amino]-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:50 N-[4-(1H-Indol-3-yl)-butyl]-4-[(thiophen-2-ylmethylene)-amino]-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:51 N-[2-(5-Methoxy-2-methyl-1H-indol-3-yl)-ethyl]-4-[(thiophen-2-ylmethylene)-amino]-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:52 N-Benzo[1,3]dioxol-5-ylmethyl-N-[2-(2-methyl-1H-indol-3-yl)-ethyl]-4-[(thiophen-2-ylmethylene)-amino]-benzamide

5:53 N-Indan-2-yl-N-(1H-indol-3-ylmethyl)-4-[(thiophen-2-ylmethylene)-amino]-benzamide

5:54 N-Benzyl-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-4-[(thiophen-2-ylmethylene)-amino]-benzamide

Example 6

This Example illustrates the potency of compounds of formula (I) and their therapeutically active acid addition salts for treatment of mental disorders.

Test 1. Affinity for the MC1-receptor

The binding assay was carried out essentially as described by Lunec et al., Melanoma Res. 1992; 2; 5-12 using I^{125}-NDP-αMSH as ligand.

Test 2. Affinity for the MC3-receptors, the MC4-receptors and the MC5-receptors

The binding assays were carried out essentially as described by Szardenings et al., J. Biol. Chem. 1997; 272; 27943-27948 and Schiöth et al., FEBS Lett. 1997; 410; 223-228 using I^{125}-NDP-αMSH as ligand.

Essentially, the affinity of the compounds for the different melanocortin receptors were determined by using either insect cells (Sf9) or COS cells, which were transfected with recombinant human MC3, MC4 or MC5 receptors. For the determination of the affinity for the MC1 receptor, B16 mouse melanoma cells were used, which endogenously express the (mouse) MC1 receptor.

The compounds were tested at different concentrations for their ability to displace a ^{125}I-labelled NDP-MSH from the respective receptor. Incubation was performed in 96-well plates, using 50,000 cells/well (Sf9 or COS cells) up to 200.000 cells/well (mouse melanoma cells).

The test compound or standard (NDP-MSH) was added in an appropriate concentration (generally between 10^{-4} M and 10^{-12} M) together with labelled tracer (approx. 50,000 cpm/well) and incubated for 2 hours (at room temperature for Sf9 cells and at +37°C for COS cells and mouse melanoma cells).

After the incubation, the cells were washed twice to get rid of the excess tracer and compound, and the cells were lysed with 0.1 M NaOH. The lysate was counted in a gamma-counter, binding was calculated and the affinity determined.

Test 3. cAMP binding assay

The stimulation of cAMP was carried out essentially as described by Schiöth et al., Br. J. Pharmacol. 1998; 124; 75-82.

Essentially, the effects of the compounds were tested in vitro for their ability to stimulate the production of cAMP. The cells used were the same as those used in

the binding studies (see above), i.e. for the MC1 receptor, mouse melanoma B16 cells were used and for the MC3, MC4 and MC5 receptors, Sf9 or COS cells, transfected with the respective human receptor, were used.

Cyclic AMP was stimulated by the addition of the compounds at different concentrations in the presence of a phosphodiesterase inhibitor, during a period of 20 minutes at +37°C. cAMP was extracted with PCA, neutralised with KOH and the mixture was then centrifuged.

The concentration of cAMP was determined using a binding assay comprising binding protein (from bovine adrenals). Tritiated cAMP, used as tracer, and extracts (from above) in different dilutions were incubated at +4°C for 120-150 minutes. The cAMP in the unknown samples displaces the labelled cAMP from binding to the binding protein. The binding protein - cAMP/tracer complex was harvested using a filter technique and the filters were counted in a beta-counter. The concentration of cAMP in the unknown extracts was calculated using a standard curve of known concentrations.

Table 1 Affinity for MC-receptors

Compound	Ki(μM)			
	MC1	MC3	MC4	MC5
1:21	0.2	2.9	4.1	7.5
1:34	0.6	5.4	2.3	28.9
2:1	30	97	38	15
2:6	2.6	57	11	13.9

Table 1b Influence on cAMP (given as percent of baseline)

	MC1c	MC4c	MC5c
2:1	328	91	89

EXAMPLE 7

Anti-inflammatory effects:

Control

Female BALB/c mice (weight 20–22 g) were sensitized by treatment of the shaved abdomen with 30 µl of 0.5% 2,4-dinitrofluorobenzene (DNFB). After 4 days they were challenged with 10 µl of 0.3 % DNFB to the paw. The unchallenged mice paws served as a control. Twenty-four hours after the last challenge, the difference in paws weight were determined as an indicator of the inflammation (paw oedema).

alpha-MSH and prednisolone controls

Mice were treated as the control but were additionally injected i.p. with α-MSH (0.5 mg/kg) or prednisolone (20 mg/kg) two hours before sensitization (day 0) and the same dose was administered repeatedly after sensitization during four consecutive days. The paw oedema inhibition was measured as described above.

Study of new Compound 2:1

Mice were treated as the control but were additionally injected i.p. with various doses (0.05, 0.15 or 0.25, 0.375, 0.5, 0.75 and in later studies also 1.5, 3 and occasionally 6 mg/kg) of each compounds two hours before sensitization (day 0) and the same dose was administered repeatedly after sensitization during four consecutive days. The paw oedema inhibition as described above. Groups containing at least 10 mice each were used for all experiments.

Blood analysis was carried out using the QBC® Autoread™ Plus & QBC® Accutube System (Becton Dickinson). In all cases blood samples were collected twenty-four hours after the last challenge.

Results:

Compound 2:1 did not significantly decrease the oedema induced in the paw, whereas there was a significant decrease in total white blood count versus untreated animals with oedema, as shown in Figures 1-2.

The following formulations are representative for all of the pharmacologically active compounds of the invention.

Example 8

Example of a preparation comprising a capsule

	Per capsule
Active ingredient, as salt	5 mg
Lactose	250 mg
Starch	120 mg
Magnesium stearate	5 mg
Total up to	385 mg

In cases higher amounts of active ingredient are required, the amount of lactose used may be reduced.

Example of a suitable tablet formulation

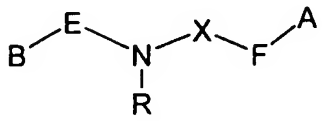
	Per tablet
Active ingredient, as salt	5 mg
Potato starch	90 mg
Colloidal Silica	10 mg
Talc	20 mg
Magnesium stearate	2 mg
5 % aqueous solution of gelatine	25 mg
Total up to	385 mg

A solution for parenteral administration by injection can be prepared in an aqueous solution of a water-soluble pharmaceutically acceptable acid addition salt of the active substance preferably in a concentration of 0.1 % to about 5 % by

weight. These solutions may also contain stabilising agents and/or buffering agents.

Claims:

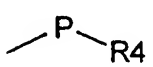
1. A compound of general formula (I)

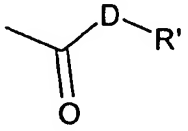


wherein X is a carbonyl, methylene or is absent (i.e. it is a single bond),

wherein E and F are independently a saturated or unsaturated, straight or branched chain acyclic hydrocarbon group having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms, preferably 1, 2, 3, 4 or 5 carbon atoms; or E and/or F may be absent;

wherein R is selected from:



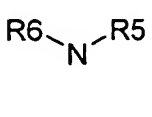
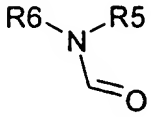


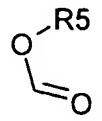
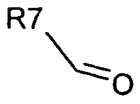
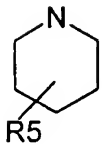
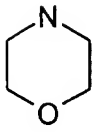
wherein P and D are independently a saturated or unsaturated, straight or branched chain acyclic hydrocarbon group having 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 carbon atoms, preferably 1, 2, 3, 4 or 5 carbon atoms, or D may be absent (i.e. D is a single bond);

R' is a hydroxy, methyl, cyclohexyl, cyclopentyl, guanidine, aminoguanidine, or carboxylic group;

R4 is a hydroxy, cyclohexyl, cyclopentyl, guanidine, aminoguanidine, or carboxylic group;

or R4 or R` may be selected from:

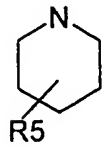
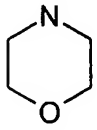



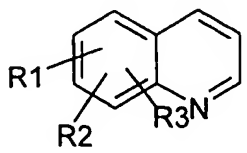
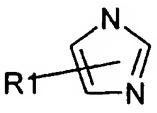

or R4 may be selected from A and B, as defined below;

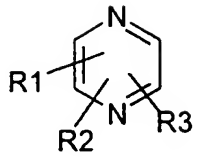
wherein R5 and R6 are the same or different and selected from hydrogen, lower alkyl such as methyl, ethyl, propyl, iso-propyl, butyl, t-butyl, pentyl, t-pentyl, iso-pentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or hexyl;

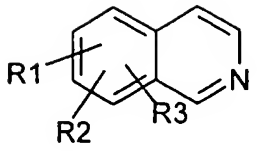
wherein R7 is selected from:

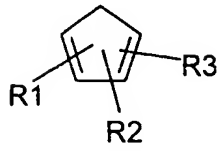



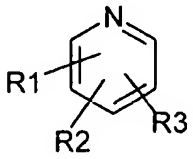

wherein A and B are independently selected from the following:

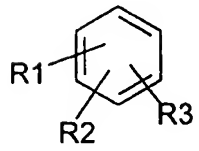



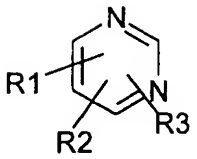


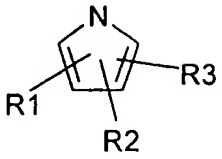


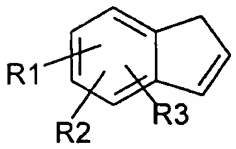


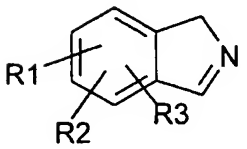


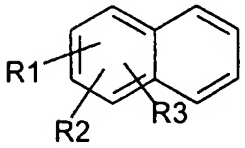


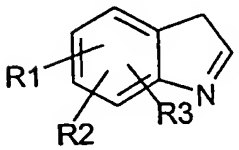












wherein R_1, R_2 and R_3 are the same or different and are selected from hydrogen, halogen, alkyl having 1 to 5 carbon atoms, electron donor groups such as alkoxy having 1-5 carbon atoms or hydroxy, electron acceptor groups selected from cyano, nitro, trifluoroalkyl or amide;

and the pharmacologically active salts thereof.

2. A compound as claimed in claim 1, wherein one or more of E, F, P and D have 1, 2, 3, 4 or 5 carbon atoms.

3. A compound as claimed in any one of the previous claims, wherein one or more of R1, R2 and R3 are alkyl having 1 to 5 carbon atoms.

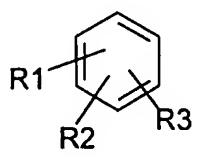
4. A compound as claimed in claim 3, wherein the alkyl is methyl or ethyl.

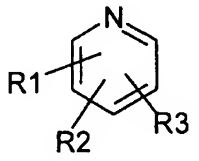
5. A compound as claimed in any one of the previous claims wherein one or more of R1, R2 and R3 are alkoxy.

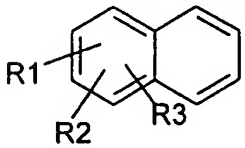
6. A compound as claimed in claim 5, wherein the alkoxy is methoxy.

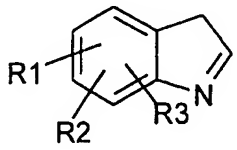
7. A compound as claimed in any one of the previous claims wherein one or more of R1, R2 and R3 are halogen atoms, preferably fluoro or chloro.

8. A compound as claimed in any one of the previous claims wherein A and B are independently selected from:









9. A compound having one of the following formulae:

1:1 N-Benzyl-N-(4-guanidino-butyl)-2-(1H-indol)-3-yl)-acetamide

1:2 N-Benzyl-N-(4-guanidino-butyl)-4-(1H-indol-3-yl)-butyramide

1:3	1H-Indole-3-carboxylic acid (2-amino-ethyl)-naphthalen-2-ylmethyl-amide
1:4	N-(2-Amino-ethyl)-2-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-acetamide
1:5	1H-Indole-5-carboxylic acid (2-amino-ethyl)-naphthalen-2-ylmethyl-amide
1:6	N-(2-Amino-ethyl)-2-(1H-indol-3-yl)-N-(1-naphthalen-2-yl-ethyl)-acetamide
1:7	N-(2-Amino-ethyl)-2-(1H-indol-3-yl)-N-(1,2,3,4-tetrahydro-naphthalen-2-yl)-acetamide
1:8	N-(2-Amino-ethyl)-2-naphthalen-2-yl-N-(1,2,3,4-tetrahydro-naphthalen-2-yl)-acetamide
1:9	N-(3-Amino-propyl)-2-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-acetamide
1:10	N-(3-Amino-propyl)-2-naphthalen-2-yl-N-naphthalen-2-ylmethyl-acetamide
1:11	N-(3-Amino-propyl)-2-(1H-indol-3-yl)-N-(3-phenyl-allyl)-acetamide
1:12	N-(3-Amino-propyl)-2-(1H-indol-3-yl)-2-oxo-N-(3-phenyl-allyl)-acetamide
1:13	1H-Indole-5-carboxylic acid (3-amino-propyl)-(3-phenyl-allyl)-amide
1:14	N-(3-Amino-propyl)-N-(2-chloro-3-phenyl-allyl)-2-(1H-indol-3-yl)-2-oxo-acetamide
1:15	1H-Indole-3-carboxylic acid (3-amino-propyl)-(2-methyl-3-phenyl-allyl)-amide
1:16	N-(3-Amino-propyl)-2-(1H-indol-3-yl)-N-(2-methyl-3-phenyl-allyl)-acetamide
1:17	N-(3-Amino-propyl)-2-(1H-indol-3-yl)-N-(2-methyl-3-phenyl-allyl)-2-oxo-acetamide
1:18	1H-Indole-3-carboxylic acid (3-amino-propyl)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amide
1:19	N-(3-Amino-propyl)-2-(1H-indol-3-yl)-N-(1,2,3,4-tetrahydro-naphthalen-2-yl)-acetamide

1:20 1H-Indole-5-carboxylic acid (3-amino-propyl)-(1,2,3,4-tetrahydro-naphthalen-2-yl)-amide

1:21 N-(3-Amino-propyl)-3-(1H-indol-3-yl)-N-(1,2,3,4-tetrahydro-naphthalen-2-yl)-propionamide

1:22 1H-Indole-3-carboxylic acid (4-amino-butyl)-naphthalen-2-ylmethyl-amide

1:23 N-(4-Amino-butyl)-2-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-acetamide

1:24 1H-Indole-5-carboxylic acid (4-amino-butyl)-naphthalen-2-ylmethyl-amide

1:25 N-(5-Amino-pentyl)-2-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-acetamide

1:26 N-(5-Amino-pentyl)-3-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-propionamide

1:27 N-(5-Amino-pentyl)-4-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-butyramide

1:28 N-[5-(4-Hydroxy-benzylamino)-pentyl]-4-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-butyramide

1:29 N-(5-Amino-pentyl)-2-(1H-indol-3-yl)-N-(1-naphthalen-2-yl-ethyl)-acetamide

1:30 N-(5-Amino-pentyl)-2-(1H-indol-3-yl)-N-[1-(4-trifluoromethyl-phenyl)-ethyl]-acetamide

1:31 N-(5-Amino-pentyl)-N-cycloheptyl-2-(1H-indol-3-yl)-acetamide

1:32 N-(5-Amino-pentyl)-N-benzo[1,3]dioxol-5-ylmethyl-4-(1H-indol-3-yl)-butyramide

1:33 N-(5-Amino-pentyl)-4-(1H-indol-3-yl)-N-(3-naphthalen-2-yl-allyl)-butyramide

1:34 N-(5-Amino-pentyl)-N-(2-chloro-3-phenyl-allyl)-4-(1H-indol-3-yl)-butyramide

1:35 N-(5-Amino-pentyl)-N-(2-chloro-3-phenyl-allyl)-3-(1H-indol-3-yl)-acrylamide

1:36 N-(5-Amino-pentyl)-4-(1H-indol-3-yl)-N-(2-methyl-3-phenyl-allyl)-butyramide

1:37 N-(5-Amino-pentyl)-3-(1H-indol-3-yl)-N-(2-methyl-3-phenyl-allyl)-acrylamide

1:38 N-(5-Amino-pentyl)-N-(4-diethylamino-benzyl)-4-(1H-indol-3-yl)-butyramide

1:39 N-(8-Amino-octyl)-3-(1H-indol-3-yl)-N-(3-phenyl-allyl)-propionamide

1:40 N-(2-Amino-ethyl)-3-(1H-indol-3-yl)-N-(3-phenyl-propyl)-propionamide

1:41 N-(3-Amino-propyl)-4-(1H-indol-3-yl)-N-phenethyl-butyramide

1:42 N-(3-Amino-propyl)-2-(1H-indol-3-yl)-N-(3-phenyl-propyl)-acetamide

1:43 N-(4-Amino-butyl)-3-(1H-indol-3-yl)-N-(3-phenyl-propyl)-propionamide

1:44 N-(5-Amino-pentyl)-2-(1H-indol-3-yl)-N-(3-phenyl-propyl)-acetamide

1:45 N-(5-Amino-pentyl)-4-(1H-indol-3-yl)-N-(3-phenyl-propyl)-butyramide

1:46 N-[4-(4-Amino-cyclohexylmethyl)-cyclohexyl]-4-(1H-indol-3-yl)-N-(3-phenyl-allyl)-butyramide

1:47 N-[4-(4-Amino-cyclohexylmethyl)-cyclohexyl]-N-benzyl-4-(1H-indol-3-yl)-butyramide

1:48 4-(1H-Indol-3-yl)-butan-2-one; compound with N1-(3-phenyl-allyl)-ethane-1,2-diamine

1:49 N-(3-Amino-propyl)-3-(1H-indol-3-yl)-N-(3-phenyl-allyl)-propionamide

1:50 N-(4-Amino-butyl)-3-(1H-indol-3-yl)-N-(3-phenyl-allyl)-propionamide

1:51 N-(5-Amino-pentyl)-3-(1H-indol-3-yl)-N-(3-phenyl-allyl)-propionamide

1:52 N-(5-Amino-pentyl)-4-(1H-indol-3-yl)-N-(3-phenyl-allyl)-butyramide

1:53 N-(3-Aminomethyl-benzyl)-4-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-butyramide

1:54 N-(3-Aminomethyl-benzyl)-N-benzyl-4-(1H-indol-3-yl)-butyramide

1:55 N-(4-Aminomethyl-benzyl)-4-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-butyramide

1:56 N-(4-Aminomethyl-benzyl)-4-(1H-indol-3-yl)-N-(3-phenyl-allyl)-butyramide

1:57 N-(2-Amino-cyclohexyl)-4-(1H-indol-3-yl)-N-(3-phenyl-allyl)-butyramide

1:58 N-(2-Guanidino-ethyl)-2-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-acetamide

1:59 N-(2-Guanidino-ethyl)-3-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-propionamide

1:60 N-(2-Guanidino-ethyl)-4-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-butyramide

1:61 N-(3-Guanidino-propyl)-2-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-acetamide

1:62 N-(3-Guanidino-propyl)-3-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-propionamide

1:63 N-(3-Guanidino-propyl)-4-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-butyramide

1:64 N-(4-Guanidino-butyl)-2-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-acetamide

1:65 N-(4-Guanidino-butyl)-3-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-propionamide

1:66 N-(4-Guanidino-butyl)-4-(1H-indol-3-yl)-N-naphthalen-2-ylmethyl-butyramide

1:67 4-(1H-Indol-3-yl)-butyric acid 3-{[(5-guanidino-pentyl)-(4-1H-indol-3-yl-butyryl)-amino]-methyl}benzylester

1:68 N-[4-(4-Guanidino-cyclohexylmethyl)-cyclohexyl]-4-(1H-indol-3-yl)-N-(3-phenyl-allyl)-butyramide

1:69 N-Benzyl-N-[4-(4-guanidino-cyclohexylmethyl)-cyclohexyl]-4-(1H-indol-3-yl)-butyramide

1:70 2-(1H-Indol-3-yl)-N-naphthalen-2-ylmethyl-N-(2-oxo-2-piperazin-1-yl-ethyl)-acetamide

1:71 2-(1H-Indol-3-yl)-N-naphthalen-2-ylmethyl-N-(3-oxo-3-piperazin-1-yl-propyl)-acetamide

2:1 [2-(1H-Indol-3-yl)-ethyl]-bis-(3-phenyl-propyl)-amine

2:2 4-Amino-N-[2-(1H-indol-3-yl)-ethyl]-N-(4-methoxy-benzyl)-butyramide

2:3 2-Amino-5-guanidino-pentanoic acid naphthalen-2-ylmethyl-naphthalen-1-ylmethyl-amide

2:4 2-Amino-5-guanidino-pentanoic acid [2-(1H-indol-3-yl)-ethyl]-naphthalen-2-ylmethyl-amide

2:5 2-Amino-5-guanidino-pentanoic acid (1H-indol-3-ylmethyl)-naphthalen-2-ylmethyl-amide

2:6 4-Guanidino-N-[2-(1H-Indol-3-yl)-ethyl]-N-(4-methoxy-benzyl)-butyramide

2:7 2-amino-N-[2-(1H-indol-3-yl)-ethyl]-N-(4-methoxy-benzyl)-acetamide

2:8 2-amino-N-benzyl-N-[2-(1H-indol-3-yl)-ethyl]-butyramide

2:9 3-amino-N-[2-(1H-indol-3-yl)-ethyl]-N-(6-phenyl-heptyl)-propionamide

2:10 8-amino-octanoic acid [2-(1H-indol-3-yl)-ethyl]-(6-phenyl-heptyl)-amide

2:11 8-amino-octanoic acid (7-phenyl-heptyl)-(6-phenyl-heptyl)-amide

3:1 2-Amino-N-[4-(1H-indol-3-yl)-butyl]-N-(3,4,5-trimethoxy-benzyl)-acetamide

3:2 2-Amino-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-N-(3,4,5-trimethoxy-benzyl)-acetamide

3:3 2-Amino-N-benzo[1,3]dioxol-5-ylmethyl-N-[2-(2-methyl-1H-indol-3-yl)-ethyl]-acetamide

3:4 2-Amino-N-indan-2-yl-N-(1H-indol-3-ylmethyl)-acetamide

3:5 2-Amino-N-benzyl-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-acetamide

3:6 2-Amino-N-benzyl-N-pyridin-3-ylmethyl-acetamide

3:7 2-Amino-N-(2-chloro-6-methyl-pyridin-3-ylmethyl)-N-indan-2-yl-acetamide

3:8 2-Amino-N-benzo[1,3]dioxol-5-ylmethyl-N-pyridin-3-ylmethyl-acetamide

3:9 2-Amino-N-(2-chloro-6-methyl-pyridin-3-ylmethyl)-N-(3,4,5-trimethoxy-benzyl)-acetamide

3:10 3-Amino-N-[4-(1H-indol-3-yl)-butyl]-N-(3,4,5-trimethoxy-benzyl)-propionamide

3:11 3-Amino-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-N-(3,4,5-trimethoxy-benzyl)-propionamide

3:12 3-Amino-N-benzo[1,3]dioxol-5-ylmethyl-N-[2-(2-methyl-1H-indol-3-yl)-ethyl]-propionamide

3:13 3-Amino-N-indan-2-yl-N-(1H-indol-3-ylmethyl)-propionamide

3:14 3-Amino-N-benzyl-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-propionamide

3:15 3-Amino-N-benzyl-N-pyridin-3-ylmethyl-propionamide

3:16 3-Amino-N-(2-chloro-6-methyl-pyridin-3-ylmethyl)-N-indan-2-yl-propionamide

3:17 3-Amino-N-benzo[1,3]dioxol-5-ylmethyl-N-pyridin-3-ylmethyl-propionamide

3:18 3-Amino-N-(2-chloro-6-methyl-pyridin-3-ylmethyl)-N-(3,4,5-trimethoxy-benzyl)-propionamide

3:19 4-Amino-N-[4-(1H-indol-3-yl)-butyl]-N-(3,4,5-trimethoxy-benzyl)-butyramide

3:20 4-Amino-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-N-(3,4,5-trimethoxy-benzyl)-butyramide

3:21 4-Amino-N-benzo[1,3]dioxol-5-ylmethyl-N-[2-(2-methyl-1H-indol-3-yl)-ethyl]-butyramide

3:22 4-Amino-N-indan-2-yl-N-(1H-indol-3-ylmethyl)-butyramide

3:23 4-Amino-N-benzyl-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-butyramide

3:24 4-Amino-N-benzyl-N-pyridin-3-ylmethyl-butyramide

3:25 4-Amino-N-(2-chloro-6-methyl-pyridin-3-ylmethyl)-N-indan-2-yl-butyramide

3:26 4-Amino-N-benzo[1,3]dioxol-5-ylmethyl-N-pyridin-3-ylmethyl-butyramide

3:27 4-Amino-N-(2-chloro-6-methyl-pyridin-3-ylmethyl)-N-(3,4,5-trimethoxy-benzyl)-butyramide

3:28 2-Guanidino-N-[4-(1H-indol-3-yl)-butyl]-N-(3,4,5-trimethoxy-benzyl)-acetamide

3:29 2-Guanidino-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-N-(3,4,5-trimethoxy-benzyl)-acetamide

3:30 N-Benzo[1,3]dioxol-5-ylmethyl-2-guanidino-N-[2-(2-methyl-1H-indol-3-yl)-ethyl]-acetamide

3:31 2-Guanidino-N-indan-2-yl-N-(1H-indol-3-ylmethyl)-acetamide

3:32 N-Benzyl-2-guanidino-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-acetamide

3:33 N-Benzyl-2-guanidino-N-pyridin-3-ylmethyl-acetamide

3:34 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-2-guanidino-N-indan-2-yl-acetamide

3:35 N-Benzo[1,3]dioxol-5-ylmethyl-2-guanidino-N-pyridin-3-ylmethyl-acetamide

3:36 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-2-guanidino-N-(3,4,5-trimethoxy-benzyl)-acetamide

3:37 4-Guanidino-N-[4-(1H-indol-3-yl)-butyl]-N-(3,4,5-trimethoxy-benzyl)-butyramide

3:38 4-Guanidino-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-N-(3,4,5-trimethoxy-benzyl)-butyramide

3:39 N-Benzo[1,3]dioxol-5-ylmethyl-4-guanidino-N-[2-(2-methyl-1H-indol-3-yl)-ethyl]-butyramide

3:40 4-Guanidino-N-indan-2-yl-N-(1H-indol-3-ylmethyl)-butyramide

3:41 N-Benzyl-4-guanidino-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-butyramide

3:42 N-Benzyl-4-guanidino-N-pyridin-3-ylmethyl-butyramide

3:43 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-4-guanidino-N-indan-2-yl-butyramide

3:44 N-Benzo[1,3]dioxol-5-ylmethyl-4-guanidino-N-pyridin-3-ylmethyl-butyramide

3:45 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-4-guanidino-N-(3,4,5-trimethoxy-benzyl)-butyramide

3:46 3-Guanidino-N-[4-(1H-indol-3-yl)-butyl]-N-(3,4,5-trimethoxy-benzyl)-propionamide

3:47 3-Guanidino-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-N-(3,4,5-trimethoxy-benzyl)-propionamide

3:48 N-Benzo[1,3]dioxol-5-ylmethyl-3-guanidino-N-[2-(2-methyl-1H-indol-3-yl)-ethyl]-propionamide

3:49 3-Guanidino-N-indan-2-yl-N-(1H-indol-3-ylmethyl)-propionamide

3:50 N-Benzyl-3-guanidino-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-propionamide

3:51 N-Benzyl-3-guanidino-N-pyridin-3-ylmethyl-propionamide

3:52 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-3-guanidino-N-indan-2-yl-propionamide

3:53 N-Benzo[1,3]dioxol-5-ylmethyl-3-guanidino-N-pyridin-3-ylmethyl-propionamide

3:54 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-3-guanidino-N-(3,4,5-trimethoxy-benzyl)-propionamide

4:1 N1-[4-(1H-Indol-3-yl)-butyl]-N1-(3,4,5-trimethoxy-benzyl)-ethane-1,2-diamine

4:2 N1-[2-(5-Methoxy-2-methyl-1H-indol-3-yl)-ethyl]-N1-(3,4,5-trimethoxy-benzyl)-ethane-1,2-diamine

4:3 N1-Benzo[1,3]dioxol-5-ylmethyl-N1-[2-(2-methyl-1H-indol-3-yl)-ethyl]-ethane-1,2-diamine

4:4 N1-Indan-2-yl-N1-(1H-indol-3-ylmethyl)-ethane-1,2-diamine

4:5 N1-Benzyl-N1-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-ethane-1,2-diamine

4:6 N1-Benzyl-N1-pyridin-3-ylmethyl-ethane-1,2-diamine

4:7 N1-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-N1-indan-2-yl-ethane-1,2-diamine

4:8 N1-Benzo[1,3]dioxol-5-ylmethyl-N1-pyridin-3-ylmethyl-ethane-1,2-diamine

4:9 N1-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-N1-(3,4,5-trimethoxy-benzyl)-ethane-1,2-diamine

4:10 N1-[4-(1H-Indol-3-yl)-butyl]-N1-(3,4,5-trimethoxy-benzyl)-propane-1,3-diamine

4:11 N1-[2-(5-Methoxy-2-methyl-1H-indol-3-yl)-ethyl]-N1-(3,4,5-trimethoxy-benzyl)-propane-1,3-diamine

4:12 N1-Benzo[1,3]dioxol-5-ylmethyl-N1-[2-(2-methyl-1H-indol-3-yl)-ethyl]-propane-1,3-diamine

4:13 N1-Indan-2-yl-N1-(1H-indol-3-ylmethyl)-propane-1,3-diamine

4:14 N1-Benzyl-N1-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-propane-1,3-diamine

4:15 N1-Benzyl-N1-pyridin-3-ylmethyl-propane-1,3-diamine

4:16 N1-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-N1-indan-2-yl-propane-1,3-diamine

4:17 N1-Benzo[1,3]dioxol-5-ylmethyl-N1-pyridin-3-ylmethyl-propane-1,3-diamine

4:18 N1-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-N1-(3,4,5-trimethoxy-benzyl)-propane-1,3-diamine

4:19 N1-[4-(1H-Indol-3-yl)-butyl]-N1-(3,4,5-trimethoxy-benzyl)-butane-1,4-diamine

4:20 N1-[2-(5-Methoxy-2-methyl-1H-indol-3-yl)-ethyl]-N1-(3,4,5-trimethoxy-benzyl)-butane-1,4-diamine

4:21 N1-Benzo[1,3]dioxol-5-ylmethyl-N1-[2-(2-methyl-1H-indol-3-yl)-ethyl]-butane-1,4-diamine

4:22 N1-Indan-2-yl-N1-(1H-indol-3-ylmethyl)-butane-1,4-diamine

4:23 N1-Benzyl-N1-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-butane-1,4-diamine

4:24 N1-Benzyl-N1-pyridin-3-ylmethyl-butane-1,4-diamine

4:25 N1-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-N1-indan-2-yl-butane-1,4-diamine

4:26 N1-Benzo[1,3]dioxol-5-ylmethyl-N1-pyridin-3-ylmethyl-butane-1,4-diamine

4:27 N1-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-N1-(3,4,5-trimethoxy-benzyl)-butane-1,4-diamine

4:28 N-{2-[[4-(1H-Indol-3-yl)-butyl]-(3,4,5-trimethoxy-benzyl)-amino]-ethyl}-guanidine

4:29 N-{2-[[2-(5-Methoxy-2-methyl-1H-indol-3-yl)-ethyl]-(3,4,5-trimethoxy-benzyl)-amino]-ethyl}-guanidine

4:30 N-(2-{Benzo[1,3]dioxol-5-ylmethyl-[2-(2-methyl-1H-indol-3-yl)-ethyl]-amino}-ethyl)-guanidine

4:31 N-{2-[Indan-2-yl-(1H-indol-3-ylmethyl)-amino]-ethyl}-guanidine

4:32 N-(2-{Benzyl-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-amino}-ethyl)-guanidine

4:33 N-[2-(Benzyl-pyridin-3-ylmethyl-amino)-ethyl]-guanidine

4:34 N-{2-[(2-Chloro-6-methyl-pyridin-3-ylmethyl)-indan-2-yl-amino]-ethyl}-guanidine

4:35 N-[2-(Benzo[1,3]dioxol-5-ylmethyl-pyridin-3-ylmethyl-amino)-ethyl]-guanidine

4:36 N-{2-[(2-Chloro-6-methyl-pyridin-3-ylmethyl)-(3,4,5-trimethoxy-benzyl)-amino]-ethyl}-guanidine

4:37 N-{4-[[4-(1H-Indol-3-yl)-butyl]-(3,4,5-trimethoxy-benzyl)-amino]-butyl}-guanidine

4:38 N-{4-[[2-(5-Methoxy-2-methyl-1H-indol-3-yl)-ethyl]-(3,4,5-trimethoxy-benzyl)-amino]-butyl}-guanidine

4:39 N-(4-{Benzo[1,3]dioxol-5-ylmethyl-[2-(2-methyl-1H-indol-3-yl)-ethyl]-amino}-butyl)-guanidine

4:40 N-{4-[Indan-2-yl-(1H-indol-3-ylmethyl)-amino]-butyl}-guanidine

4:41 N-(4-{Benzyl-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-amino}-butyl)-guanidine

4:42 N-[4-(Benzyl-pyridin-3-ylmethyl-amino)-butyl]-guanidine

4:43 N-{4-[(2-Chloro-6-methyl-pyridin-3-ylmethyl)-indan-2-yl-amino]-butyl}-guanidine

4:44 N-[4-(Benzo[1,3]dioxol-5-ylmethyl-pyridin-3-ylmethyl-amino)-butyl]-guanidine

4:45 N-{4-[(2-Chloro-6-methyl-pyridin-3-ylmethyl)-(3,4,5-trimethoxy-benzyl)-amino]-butyl}-guanidine

4:46 N-{3-[[4-(1H-Indol-3-yl)-butyl]-(3,4,5-trimethoxy-benzyl)-amino]-propyl}-guanidine

4:47 N-{3-[[2-(5-Methoxy-2-methyl-1H-indol-3-yl)-ethyl]-(3,4,5-trimethoxy-benzyl)-amino]-propyl}-guanidine

4:48 N-(3-{Benzo[1,3]dioxol-5-ylmethyl-[2-(2-methyl-1H-indol-3-yl)-ethyl]-amino}-propyl)-guanidine

4:49 N-{3-[Indan-2-yl-(1H-indol-3-ylmethyl)-amino]-propyl}-guanidine

4:50 N-(3-{Benzyl-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-amino}-propyl)-guanidine

4:51 N-[3-(Benzyl-pyridin-3-ylmethyl-amino)-propyl]-guanidine

4:52 N-{3-[(2-Chloro-6-methyl-pyridin-3-ylmethyl)-indan-2-yl-amino]-propyl}-guanidine

4:53 N-[3-(Benzo[1,3]dioxol-5-ylmethyl-pyridin-3-ylmethyl-amino)-propyl]-guanidine

4:54 N-{3-[(2-Chloro-6-methyl-pyridin-3-ylmethyl)-(3,4,5-trimethoxy-benzyl)-amino]-propyl}-guanidine

5:1 2,3,4-Trihydroxy-N-[4-(1H-indol-3-yl)-butyl]-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:2 2,3,4-Trihydroxy-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:3 N-Benzo[1,3]dioxol-5-ylmethyl-2,3,4-trihydroxy-N-[2-(2-methyl-

1H-indol-3-yl)-ethyl]-benzamide

5:4 2,3,4-Trihydroxy-N-indan-2-yl-N-(1H-indol-3-ylmethyl)-benzamide

5:5 N-Benzyl-2,3,4-trihydroxy-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-benzamide

5:6 3-Dimethylamino-N-[4-(1H-indol-3-yl)-butyl]-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:7 3-Dimethylamino-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:8 N-Benzo[1,3]dioxol-5-ylmethyl-3-dimethylamino-N-[2-(2-methyl-1H-indol-3-yl)-ethyl]-benzamide

5:9 3-Dimethylamino-N-indan-2-yl-N-(1H-indol-3-ylmethyl)-benzamide

5:10 N-Benzyl-3-dimethylamino-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-benzamide

5:11 4-Ethoxy-N-[4-(1H-indol-3-yl)-butyl]-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:12 4-Ethoxy-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:13 N-Benzo[1,3]dioxol-5-ylmethyl-4-ethoxy-N-[2-(2-methyl-1H-indol-3-yl)-ethyl]-benzamide

5:14 4-Ethoxy-N-indan-2-yl-N-(1H-indol-3-ylmethyl)-benzamide

5:15 N-Benzyl-4-ethoxy-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-benzamide

5:16 2-Hydroxy-N-[4-(1H-indol-3-yl)-butyl]-6-isopropyl-3-methyl-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:17 2-Hydroxy-6-isopropyl-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-3-methyl-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:18 N-Benzo[1,3]dioxol-5-ylmethyl-2-hydroxy-6-isopropyl-3-methyl-N-[2-(2-methyl-1H-indol-3-yl)-ethyl]-benzamide

5:19 2-Hydroxy-N-indan-2-yl-N-(1H-indol-3-ylmethyl)-6-isopropyl-3-methyl-benzamide

5:20 N-Benzyl-2-hydroxy-6-isopropyl-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-3-methyl-benzamide

5:21 2-Fluoro-N-[4-(1H-indol-3-yl)-butyl]-5-methyl-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:22 2-Fluoro-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-5-methyl-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:23 N-Benzo[1,3]dioxol-5-ylmethyl-2-fluoro-5-methyl-N-[2-(2-methyl-1H-indol-3-yl)-ethyl]-benzamide

5:24 2-Fluoro-N-indan-2-yl-N-(1H-indol-3-ylmethyl)-5-methyl-benzamide

5:25 N-Benzyl-2-fluoro-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-5-methyl-benzamide

5:26 N-Benzyl-2,3,4-trihydroxy-N-pyridin-3-ylmethyl-benzamide

5:27 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-2,3,4-trihydroxy-N-indan-2-yl-benzamide

5:28 N-Benzo[1,3]dioxol-5-ylmethyl-2,3,4-trihydroxy-N-pyridin-3-ylmethyl-benzamide

5:29 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-2,3,4-trihydroxy-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:30 N-Benzyl-3-dimethylamino-N-pyridin-3-ylmethyl-benzamide

5:31 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-3-dimethylamino-N-indan-2-yl-benzamide

5:32 N-Benzo[1,3]dioxol-5-ylmethyl-3-dimethylamino-N-pyridin-3-ylmethyl-benzamide

5:33 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-3-dimethylamino-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:34 N-Benzyl-4-ethoxy-N-pyridin-3-ylmethyl-benzamide

5:35 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-4-ethoxy-N-indan-2-yl-benzamide

5:36 N-Benzo[1,3]dioxol-5-ylmethyl-4-ethoxy-N-pyridin-3-ylmethyl-benzamide

5:37 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-4-ethoxy-N-(3,4,5-

trimethoxy-benzyl)-benzamide

5:38 N-Benzyl-2-hydroxy-6-isopropyl-3-methyl-N-pyridin-3-ylmethyl-benzamide

5:39 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-2-hydroxy-N-indan-2-yl-6-isopropyl-3-methyl-benzamide

5:40 N-Benzo[1,3]dioxol-5-ylmethyl-2-hydroxy-6-isopropyl-3-methyl-N-pyridin-3-ylmethyl-benzamide

5:41 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-2-hydroxy-6-isopropyl-3-methyl-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:42 N-Benzyl-2-fluoro-5-methyl-N-pyridin-3-ylmethyl-benzamide

5:43 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-2-fluoro-N-indan-2-yl-5-methyl-benzamide

5:44 N-Benzo[1,3]dioxol-5-ylmethyl-2-fluoro-5-methyl-N-pyridin-3-ylmethyl-benzamide

5:45 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-2-fluoro-5-methyl-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:46 N-Benzyl-N-pyridin-3-ylmethyl-4-[(thiophen-2-ylmethylene)-amino]-benzamide

5:47 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-N-indan-2-yl-4-[(thiophen-2-ylmethylene)-amino]-benzamide

5:48 N-Benzo[1,3]dioxol-5-ylmethyl-N-pyridin-3-ylmethyl-4-[(thiophen-2-ylmethylene)-amino]-benzamide

5:49 N-(2-Chloro-6-methyl-pyridin-3-ylmethyl)-4-[(thiophen-2-ylmethylene)-amino]-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:50 N-[4-(1H-Indol-3-yl)-butyl]-4-[(thiophen-2-ylmethylene)-amino]-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:51 N-[2-(5-Methoxy-2-methyl-1H-indol-3-yl)-ethyl]-4-[(thiophen-2-ylmethylene)-amino]-N-(3,4,5-trimethoxy-benzyl)-benzamide

5:52 N-Benzo[1,3]dioxol-5-ylmethyl-N-[2-(2-methyl-1H-indol-3-yl)-ethyl]-4-[(thiophen-2-ylmethylene)-amino]-benzamide

5:53 N-Indan-2-yl-N-(1H-indol-3-ylmethyl)-4-[(thiophen-2-ylmethylene)-amino]-benzamide

5:54 N-Benzyl-N-[2-(5-methoxy-2-methyl-1H-indol-3-yl)-ethyl]-4-[(thiophen-2-ylmethylene)-amino]-benzamide

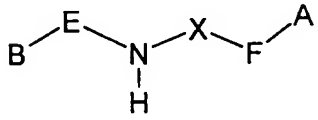
or a pharmaceutically acceptable salt thereof.

10. A compound as claimed in any one of the previous claims which additionally comprises a label, preferably a radioactive label, or a toxic agent.

11. A pharmaceutical composition comprising a compound as claimed in any one of claims 1 to 10 together with one or more adjuvants, carriers or excipients.

12. A compound as claimed in any one of claims 1 to 10 for use as a medicament.

13. A process for the production of a compound as claimed in any one of claims 1 to 10 which comprises reacting a compound of formula (III) with a compound of formula (II), preferably using a standard N-alkylation procedure



(II)

(III)

wherein Y is a suitable leaving group.

14. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for the treatment of inflammation.

15. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for the treatment of mental disorders.

16. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for the treatment of dysfunctions of the endocrine system or an hormonal system.

17. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for the treatment of sexual functions and/or sexual dysfunctions.

18. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for the treatment of drug-induced disorders of the blood and/or lymphoid system.

19. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for the treatment of allergic disorders.

20. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for the treatment of disorders of the cardiovascular system.

21. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for the treatment of pain.

22. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for inducing skin tanning or for inducing lighter skin colour.

23. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for the treatment of diabetes type II.

24. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for the treatment of obesity.

25. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for the treatment of anorexic conditions such as those caused by cancer, cachexia, geriatric conditions, HIV, trauma and psychological conditions.

26. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for inducing peripheral nerve regeneration.

27. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for inducing central nerve regeneration.

28. A method of treating inflammation comprising the use or administration of a compound as claimed in any one of claims 1 to 10.

29. A method of treating mental disorders comprising the use or administration of a compound as claimed in any one of claims 1 to 10.

30. A method of treating dysfunctions of the endocrine system or an hormonal system comprising the use or administration of a compound as claimed in any one of claims 1 to 10.

31. A method of treating sexual functions and/or sexual dysfunctions comprising the use or administration of a compound as claimed in any one of claims 1 to 10.

32. A method of treating drug-induced disorders of the blood and/or lymphoid system comprising the use or administration of a compound as claimed in any one of claims 1 to 10.

33. A method of treating disorders of the cardiovascular system comprising the use or administration of a compound as claimed in any one of claims 1 to 10.

34. A method of treating pain comprising the use or administration of a compound as claimed in any one of claims 1 to 10.

35. A method of inducing skin tanning or for inducing lighter skin colour comprising the use or administration of a compound as claimed in any one of claims 1 to 10.

36. A method of treating diabetes type II comprising the use or administration of a compound as claimed in any one of claims 1 to 10.

37. A method of treating obesity comprising the use or administration of a compound as claimed in any one of claims 1 to 10.

38. A method of treating anorexic conditions such as those caused by cancer, cachexia, geriatric conditions, HIV, trauma and psychological conditions comprising the use or administration of a compound as claimed in any one of claims 1 to 10.

39. A method of inducing peripheral nerve regeneration comprising the use or administration of a compound as claimed in any one of claims 1 to 10.

40. A method of inducing central nerve regeneration comprising the use or administration of a compound as claimed in any one of claims 1 to 10.

41. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for the treatment of skin disorders, including for the treatment of melanoma.

42. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for the treatment and/or diagnosis of malignancies, such as melanoma and metastases.

43. A method of treating a skin disorder, including the treatment of melanoma, comprising the use or administration of a compound as claimed in any one of claims 1 to 10.

44. A method of treating and/or diagnosing malignancies, such as melanoma and metastases, comprising the use or administration of a compound as claimed in any one of claims 1 to 10.

45. Use of a compound as claimed in any one of claims 1 to 10 in the production of a medicament for the treatment of ischemia and/or ischemia/reperfusion.

46. A method of treating ischemia and/or ischemia/reperfusion comprising the use or administration of a compound as claimed in any one of claims 1 to 10.

Figure 1

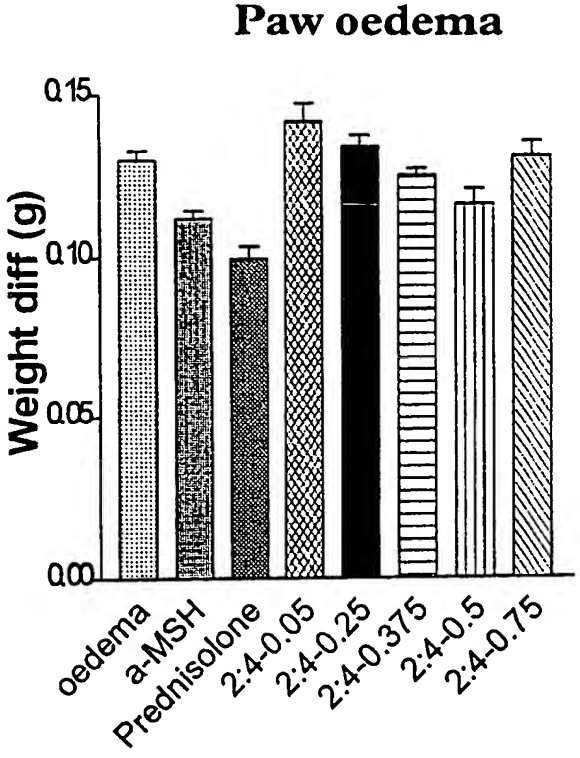


Figure 2